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EXPERIMENTAL HEART DISEASE*

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ONE of the great developments in clinical medicine of the past twenty years is the distinction between attacks of angina pectoris and attacks of coronary thrombosis. Even as late as 1923, Sir James Mackenzie did not make clinical diagnoses of coronary thrombosis.

Dock in 1896 was perhaps the first to report an instance of coronary thrombosis diagnosed ante-mortem and proved at autopsy. Huchard in 1899, in a pathological study of 185 fatal cases of angina pectoris, paid close attention to the coronary artery and noted the frequency of coronary thrombosis. Krehl (1901) called attention to the possibility of recovery after an attack of coronary thrombosis and suggested that the symptoms would be much more likely to be severe if the vessels were occluded suddenly than when sclerosis of the coronary artery was more diffuse and gradual in its development.

Obratzow and Strascheski (1910) gave the first important description of the clinical features of coronary thrombosis and diagnosed two of the three cases published. They pointed out the different pathological, as well as clinical pictures which might result, depending upon the size of the involved coronary artery.

Herrick (1912) was one of the first to show that cases of myocardial infarction could be diagnosed clinically, and that all cases were not fatal. In 1912 he stressed the point that coronary thrombosis was a clinical entity, could be diagnosed during life, and that it was not necessarily fatal. Herrick (1918, 1919) again contributed to this subject and tried to stress the importance of coronary thrombosis as a clinical disease—and one which should be diagnosed. To him must be given the credit for popularizing the diagnosis of the clinical entity of coronary thrombosis on this continent.

From 1920 to 1926 and more recently 1932 to 1937, many excellent papers and books have been written on the clinical aspect of this condition;

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these publications have facilitated the diagnosis of coronary thrombosis (Pardee, 1920; Levine, 1929; Levy, 1929; White, 1931; Sutton and Lueth, 1932; Cowdry, 1933; Oille, 1933, etc.). (See Hall, 1936.)

In a similar manner the pathological changes which occur in the coronary arteries and the subsequent changes in myocardium have been studied by many investigators, and the pathological sequence of events is well recognized. Likewise, from the work of Gross (1921), Spalteholz (1924) and Ehrich, de la Chapelle and Cohn (1931), etc., the distribution and anastomoses of the coronary arteries in man have been accurately described. That the anastomosis between the right and left coronary arteries increases with advancing age has been demonstrated by Gross, Epstein and Kugel (1934). They further showed that this ever increasing anastomosis is further increased by any gradual narrowing of the lumen. Thus the heart, in the sixth and seventh decades, is comparatively well able to survive a progressive occlusion of one or more branches of a coronary artery.

After being able to diagnose the disease and treat the patient clinically, and at the same time appreciate the pathological changes involved, the most important phase at the present time is to understand the nature and the cause of the disease.

A great deal of information concerning "heart disease" has been obtained from experimental occlusion of various branches of the coronary arteries. Experiments of this nature have been carried out almost continuously from the time of Erichsen (1844) and Panum (1862). Cohnheim was the first to make a complete investigation of this phase of cardiac physiology and in 1881 published a comprehensive report on the effects of coronary artery occlusion. Since that time many hundreds of papers have contributed further to our knowledge of the sequelae of coronary occlusion. All of these effects of occlusion are due to a reduction of the blood supply to the myocardium. It is obvious, then, that one must attempt to investigate the factors which would tend to produce either acute or chronic narrowing of the lumen of the coronary vessels, local or general, and the subsequent ischemia of the heart muscles.

Studies on the effects of anoxemia on heart muscle have been reported. Wertheimer (1930) showed that the perfused beating heart maintained its glycogen content so long as sufficient oxygen was supplied. Long and Evans (1932) then proved that anoxemia resulted in a very rapid depletion of the heart glycogen. Himwick, Koskoff and Nahum (1928), Veischer and Mulder (1930) and McGinty (1931) have, in turn, shown that lactic acid and glucose are removed from the blood by the normal heart and converted into glycogen. Himwick, Goldfarb and Nahum (1934) have shown that following coronary occlusion, the infarcted area loses fairly large quantities of glycogen which produce, in turn, an increase in lactic acid and soluble carbohydrates. The infarcted area, which showed a lowered glycogen concentration, contained an average of 260 mg. per cent less than the normal areas.

The lactic acid content of tissues remains low and the glycogen high when the oxygen supply is adequate, but when the oxygen tension is decreased, or in the absence of oxygen, the glycogen decreases and the lactic acid increases. The contractile power of skeletal muscle is lost when the lactic acid increases to 300 mg. per cent, whereas in cardiac muscle, being much more sensitive, fatigue and loss of contractility result when the concentration increases to 70 mg. per cent (Katz and Long, 1925 to 1926). Thus acute anoxemia of the myocardium results in a local increase of lactic acid at the expense of the glycogen, an increase which in some cases exceeds the level where the contraction response could occur (Grayzel, etc., 1934, and Himwick, etc., 1934).

Lewis, Pickering and Rothschild (1930) have shown that a decrease of the blood supply to skeletal muscle, which gave rise to an increased concentration of lactic acid, produced subjective symptoms of pain. The suggestion has been made (Himwick, 1934) that the accumulation of metabolites in the infarcted area of myocardium following coronary occlusion might be the cause of the subjective pain as experienced by patients in angina or during coronary occlusion.

In order to appreciate fully the factors which might influence the degree of ischemia, it is necessary to consider the physiological regulations of coronary blood flow, the effect of altered rhythms and rates, the influence of chemical factors and the effect of metabolites on the oxygen utilization by heart muscle. These physiological considerations have been reviewed by the author (1936).

Assuming that the innervation of the heart and its blood vessels is normal and that other non-local influences are not affecting the mechanics of the heart, we may assume that the normal functioning of the heart depends upon the integrity of its own blood vessels. This in turn depends upon the ability of the coronary arteries to respond to normal physiological stimuli by a change in tone of the vessel wall, whether this be dilatation or constriction. The inability of the coronary vessels to respond normally to efferent stimuli limits the functional capacity of the heart itself and relative degrees of ischemia may result. There are, of course, certain conditions which decrease the blood supply to the heart muscle in the presence of normal coronary arteries. These, as White (1934) points out, are " severe anemia, marked aortic regurgitation, extreme bradycardia, extreme tachycardia, marked temporary hypertension, and blocking of the mouths of the coronary arteries by large vegetations on the aortic valve or by syphilitic aortitis." Otherwise a reduction in the blood supply is usually the result of obstruction or narrowing of the coronary arteries. Narrowing is most commonly the result of atheromatous changes in the vessel wall with subsequent diminution in the size of the lumen. The obstruction may be the result of thrombosis, due to the deposition of platelets, fibrin and cells upon a damaged intima or upon an atheromatous plaque. Sudden occlusion may be the result of thrombi or even plaques breaking

loose from the wall of a larger sized coronary artery and causing occlusion of an artery distal to the initial lesion. Other pathological considerations have been reviewed by the author (1936).

We know then that the clinical entity of "coronary disease" and the pathological changes in myocardium are due to a diminution of the blood supply to the heart muscle and that such diminution is the result of narrowing or obstruction of the coronary arteries by degenerative changes in the vessel walls. Let us consider, then, the factors which are responsible for the degenerative lesions in the coronary arteries.

Many theories have been advanced as to the cause of, or the nature of development of atheroma of the coronary arteries and of arteriosclerosis in general. The inflammatory origin and the suggestion that the changes in the coronary arteries as seen in acute infections are the precursors of arteriosclerosis have to be carefully considered. However, this conception must be only a small factor in the ultimate serious manifestations of coronary disease. On the other hand, certain types of arterial lesions can be produced in rabbits by high protein feeding (Newburgh and Clarkson, 1922, 1923). Hypersuprarenalemia has also been shown (Danisch, 1928) to be an important factor in the cause and development of arteriosclerotic changes. Experimental adrenalin sclerosis has been recorded many times (Thorel, 1915; Cowdry, 1933). Excessive feeding of cholesterol and cholesterol-like substances also has been found to produce arterial lesions in rabbits. This subject has been extended and reviewed by Duff (1935). Joslin (1927) and others have suggested that the high incidence of arteriosclerosis in diabetic patients may be due to an "incomplete oxidation of fats." Arterial changes following the administration of excessive amounts of vitamin D have been reported on by Vanderveer (1931), Ham (1934), etc.

Obviously, then, the cause of the arterial degenerations is unknown.

Although diet, climate, race, etc. appear to have little influence on the incidence of coronary disease, it is nevertheless, much more frequent in males than in females (White and Jones, 1928; Parkinson and Bedford, 1928), and it seems that the high-strung, worried, business and professional man is more susceptible to the disease than is the placid, insensitive individual. This fact in itself should suggest a neurophysiological influence.

It was on this basis that the experiments to be reported were carried out.

Under normal conditions we may assume that the sympathetic and parasympathetic divisions of the autonomic nervous system, which are synergistic in function, are in equilibrium. Further, we may assume that any disturbance of the physiological balance of these nerves may eventually result in pathological changes in the dually innervated organs.

Physiological dysfunction of a group of central nuclei may produce a symptom-complex, from an increase in functional activity in the respective divisions of the autonomic nervous system, which may affect the whole nervous system or only a special localized part of it. Exaggerated "tonus" or "status" of either system does not necessarily imply hyperirritability or

physiological dysfunction of the nerve centers involved, but these may be produced by an excess, either relative or absolute, of stimulating substances in the blood.

In the intact animal the effects of vagus or parasympathetic stimulation are produced through the medium of liberated or synthesized acetylcholine. The parasympathetic nerves are therefore spoken of as cholinergic. In a similar manner the effects of sympathetic nerve stimulation are produced through the medium of a liberated adrenalin-like substance and these postganglionic sympathetic nerves are therefore spoken of as adrenergic nerves. This is true only of the postganglionic sympathetic fibers, since an impulse passing along a preganglionic sympathetic fiber liberates acetylcholine at the synapse in the sympathetic ganglia before the impulse is transmitted through the ganglia to the adrenergic postganglionic fibers. With parasympathetic fibers both pre- and post-ganglionic fibers are cholinergic.

Thus we find that acetylcholine is being liberated constantly in the body producing its effects on all dually innervated organs.

The effect of acetylcholine, whether produced by vagus stimulation or by intravenous injection of the autacoid, is evanescent, due to the very rapid hydrolysis of the acetylcholine by a more or less specific choline-esterase (Stedman, etc., 1933) which is present in the circulating blood and other tissues of the body. In general, too, the effects of parasympathetic excitation are inhibited by atropine and enhanced by eserine, the eserine being effective through its inhibition of the choline-esterase. Thus the regulation of the whole parasympathetic division of the autonomic nervous system depends upon the integrity of the acetylcholine-esterase mechanism (Hall and Ettinger, 1937; Hall and Lucas, 1937).

It seemed reasonable, therefore, that a functional imbalance of the two divisions of the autonomic nervous system might result from long-continued daily intravenous injections of this vagomimetic substance, acetylcholine, a substance which occurs naturally and continuously in the body.

Experimental

Acetylcholine solution, 1:10,000, was injected intravenously into unanesthetized dogs. Sterile technic was used. The daily injection period was 90 minutes, during which time the animal received 50 mg. of acetylcholine (approximately 4 mg. per kilo. body weight) in 500 c.c. of isotonic saline. Daily injections, seven days a week, were continued until the death of the animal.

In the hope of correlating any clinical symptoms with the experimental results, routine laboratory procedures were carried out on each dog each week (Hall, Ettinger and Banting, 1936). Fatal coronary artery and myocardial damage was produced in these dogs after receiving 25 to 226 (in two dogs over 400) continuous daily injections of acetylcholine; two young dogs receiving similar injections died from gastrointestinal disturbances

(Banting and Hall, 1937). In the older dogs the arterial damage was more marked than in the younger dogs, although in all cases clinical evidence of progressive myocardial failure with subsequent death was noted. Such evidence included attacks characterized by restlessness and distress, leukocytosis, elevated temperature, dyspnea, decreased blood pressure and changing electrocardiograms.

One of the earliest changes observed in the electrocardiogram was a prolongation of the PR interval even up to 0.4 second. Frequently the QRS interval was irregularly increased usually in association with ventricular extrasystoles. The extrasystoles often appeared in bouts of four or five (figure 1a) but more frequently appeared singly. The point of origin of these ectopic beats could not be determined from the electrocardiogram.

After an " attack " the electrocardiogram usually showed an irregularity in voltage of the R-wave with the tendency for a deeply negative T to be associated with an increased voltage of the corresponding R. In these instances the QRS interval was prolonged. Quite frequently complete and partial heart block was evident, there often being as many as six or eight missed beats, to be followed almost invariably by a 2 : 1 block with abnormal T-waves (figure 1b). Often following an " attack " the T-waves became completely inverted (figure 1c). The variable shape and voltage of the T-waves, at the same time considering the degree of myocardial failure exhibited by these animals, suggests a decrease in blood supply to heart muscle with resulting cardiac infarction. The great regularity with which auricular fibrillation was recorded in these animals (figure 1d) again suggests a grade of heart disease. Auricular ectopic beats were infrequently noted.

Examination of routine sections of the heart showed areas of early hyaline degeneration of myocardium (figure 2), recent infarcts of myocardium, including papillary muscles (figure 3), hyaline degeneration of the media of the medium and smaller sized arteries, thrombosis of branches of coronary artery, recanalization of occluding thrombi (figure 4), fatty degeneration of myocardium in the region of infarction and areas of fibrosis (figure 5).

It is interesting to note here that almost all the younger animals under the influence of exaggerated parasympathetic tone exhibited melena and hematemesis and at autopsy showed congestion of the mucosa in the stomach and duodenum, and in several cases ulceration had occurred. Inhibition of parasympathetic overactivity by atropine prevented the occurrence of such lesions. Eserine, on the other hand, enhanced the acetylcholine and vagal effects (Manning, Hall and Banting, 1937).

Control experiments have been carried out and reported by Hall, Ettinger and Banting, 1936; Banting and Hall, 1937; Manning, Hall and Banting, 1937, etc., and no abnormal clinical pathological manifestations were observed.

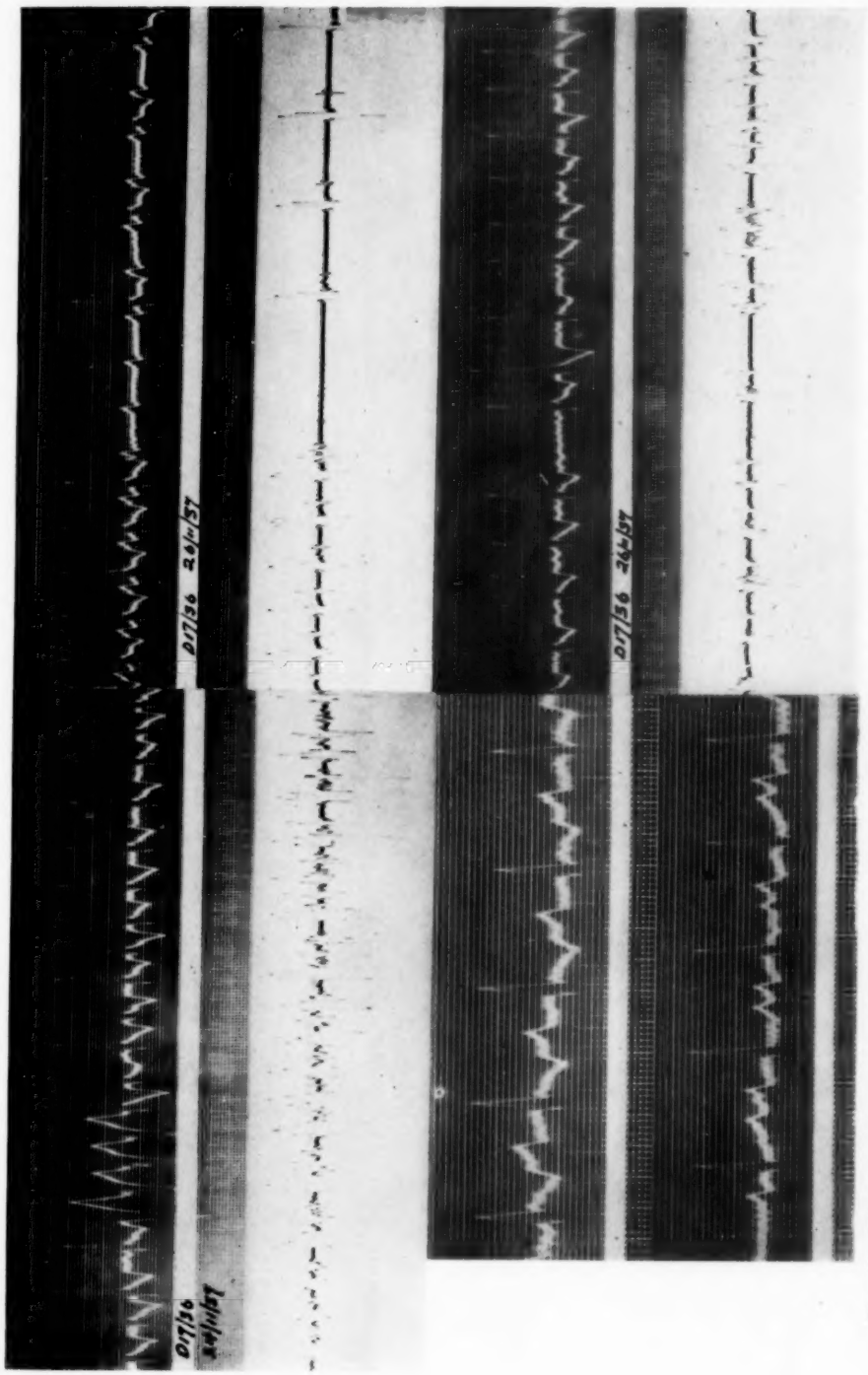

FIG. 1. Electrocardiographic changes induced in dogs by repeated injections of acetylcholine. (*a*) (Upper left) Extrasystoles; (*b*) (Upper right) Heart block; (*c*) (Lower left) Inversion of T-wave; (*d*) (Lower right) Auricular fibrillation. Ectopic foci, ventricular.

FIG. 2. Early hyaline degeneration of the myocardium.

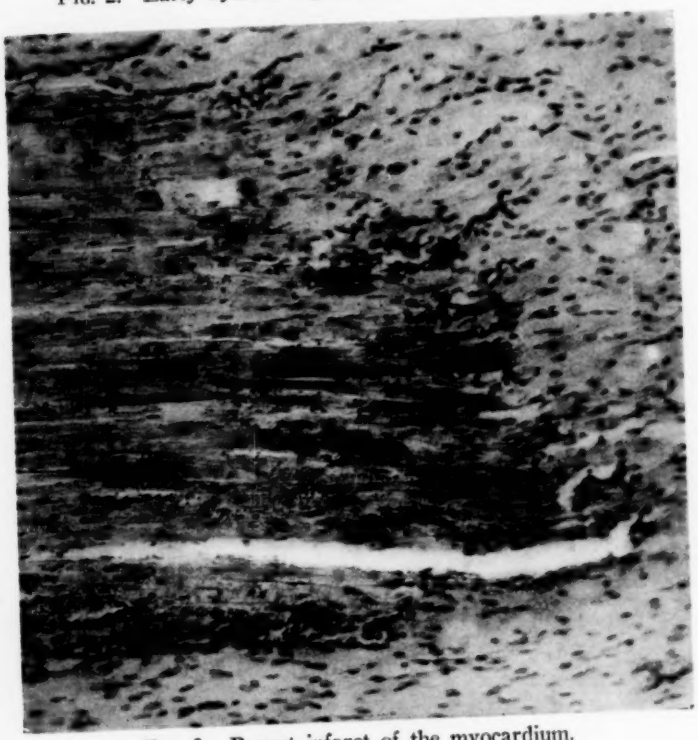

FIG. 3. Recent infarct of the myocardium.

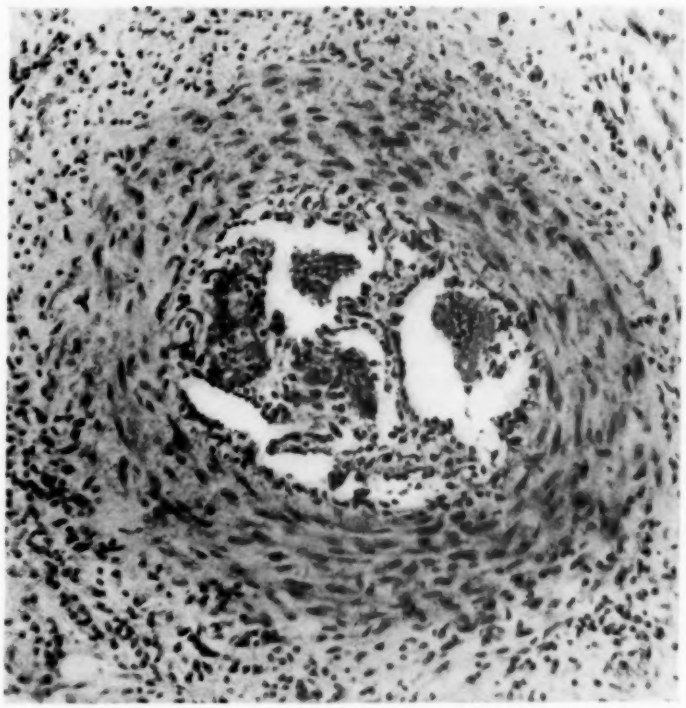

FIG. 4. Thrombosis of coronary artery with recanalization.

FIG. 5. Area of fibrosis in old infarct.

In order to show the similarity between the pathological changes in the myocardium of these dogs with those produced by actual ligation of the coronary arteries, Hall and Manning (1938) ligated the left anterior descending branch of the coronary artery at the same point in eight litter-mate puppies. The pups were sacrificed 6 hours, 12 hours, 24 hours, 48 hours, 3 days, 7 days, 14 days and 21 days after occlusion. In another series the left circumflex branch was ligated in six litter-mate pups. These were sacrificed 12 hours, 24 hours, 48 hours, 3 days, 7 days and 14 days after occlusion. The right coronary artery was similarly ligated in another series of litter-mate pups.

The earliest change observed in heart sections from these animals was a diffuse hyaline degeneration—the nuclei still staining well. In the next 24 hours the infarcted area became more well defined—the ischemic muscle fibers staining poorly and showing loss of striations. In the 48 hour sections fibrous tissue cells are seen and within 72 hours the fibrosis is well developed. Sections taken 7, 14 and 21 days after ligation show the progressive development of the fibrosis with the formation of macroscopic scars.

The similarity between the myocardial changes as observed in the dogs dying of "coronary disease" and in those killed after varying periods of acute coronary occlusion is striking.

In the original hypothesis it was intimated that the effects of physiological dysfunction might be evidenced by pathological changes in one or more local areas. This has been demonstrated experimentally by producing an autonomic imbalance by the exaggeration of parasympathetic effects.

Secondly, then, the effects of producing essentially the same type of autonomic imbalance by a relative decrease in sympathetic tone will be considered.

It has been recorded by Banting and Gairns (1926) and others, that duodenal and gastric ulcerations with hematemesis, melena, etc. commonly occur in adrenalectomized dogs. In view of the sympathetic failure in adrenal insufficiency, described first by Elliott (1914) and more recently by Cleghorn (1937, 1938), this might be considered a parasympathetic effect, resembling as it does so closely the lesions observed by Hall, Ettinger and Banting (1936). If this were so it might be expected that cardiac changes as found by these authors, might be met in animals dying of adrenal insufficiency. No reference has been found, however, describing the occurrence or even intimating the possibility of cardiac lesions and few referring to cardiac dysfunction in experimental adrenal insufficiency.

The close examination of the hearts of animals dying of adrenal insufficiency, however, revealed cardiac lesions. This finding, which apparently had not been previously described, was reported in brief by Banting and Hall (1937) and by Hall and Cleghorn (1937), who showed electrocardio-

graphic and kymographic evidence of marked cardiac dysfunction as a result of suppression of sympathetic effects.

More recently Hall and Cleghorn (1938) have reported more fully on this subject. The animals (dogs) used were bilaterally adrenalectomized in two stages. Post-operative treatment included intravenous normal saline and cortical extract, followed by subcutaneous injections of the hormone twice daily until the animal was gaining weight and was otherwise in good health. At this time a series of normal electrocardiograms was taken and chemical estimations of blood were made. The administration of cortical extract was then discontinued. During the period of insufficiency routine examinations of blood were made; electrocardiograms were taken with increasing frequency as the clinical condition of the animals became progressively more grave.

Periodically throughout the stage of insufficiency evidence of dyspnea and distress was noted. Frequently, too, coarse râles were heard following such an attack. This pulmonary edema was usually evident at autopsy.

Extrasystoles, cardiac irregularity, changing T-waves, extreme bradycardia followed by a marked pulse deficit and at times associated with the complete absence of P-waves indicated a definite cardiac dysfunction. The failure of the heart of these animals to accelerate following atropine indicated the inability of the sympathetic mechanism to assume control when vagal influences were suppressed.

In histological sections taken from the hearts of these animals arterial and myocardial damage was seen. In some sections recent thrombus formation was observed with its attachment to vessel wall at the site of a break in the continuity of the endothelial lining. Other sections showed arteries whose walls were markedly edematous and in some cases arterial spasm was evident. (Figure 6.) Complete thrombosis of a number of medium-sized coronary arteries was also noted and in a few instances (figure 7) organization and recanalization of the thrombus had taken place. In two cases degeneration of the media of larger-sized coronary arteries was observed. Early hyaline degenerative changes were seen in sections of myocardium.

Macroscopic ulcers were frequently found in the duodenum and prepyloric region of the stomach.

Essentially the same kind of experiments has been reported by Bodansky and Brindley (1937) in confirming our work, in which they produced myocardial degeneration and endothelial proliferation of the coronary vessels in rats following 85 to 90 daily subcutaneous injections of acetylcholine.

Hall (1938) again showed that myocardial and coronary artery changes were produced by the daily injection of acetylcholine in rats and rabbits. Of greatest interest was the preponderance of peripheral arterial lesions in rats following the daily injection of acetylcholine for periods up to 400 days. The process consists, in the aorta, of an intimal thickening with a prolifera-

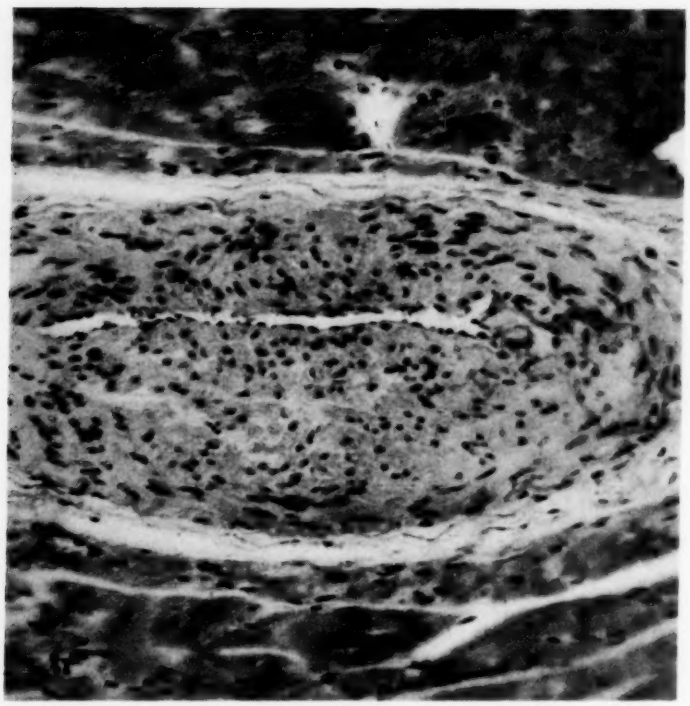

FIG. 6. Spasm of coronary artery—with thickening. Adrenalectomized dog.

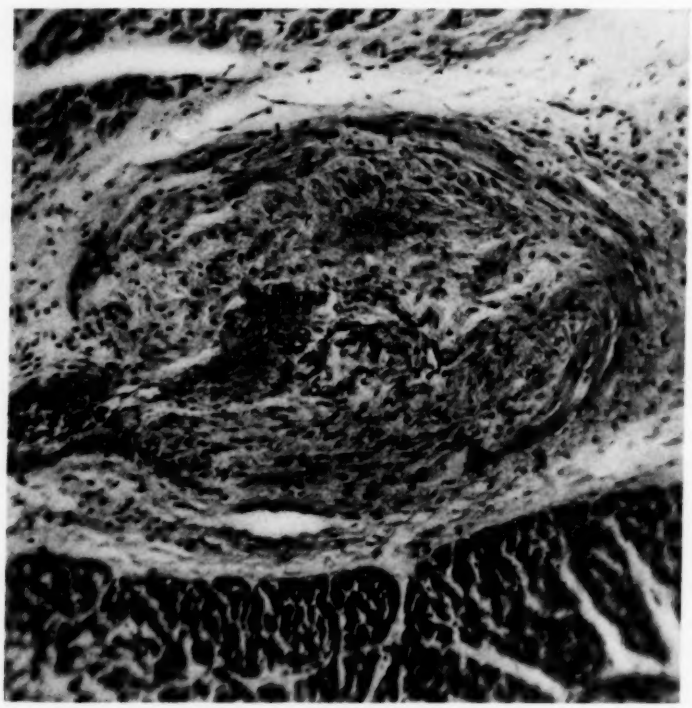

FIG. 7. Complete occlusion of the coronary artery with some organization. Adrenalectomized dog.

FIG. 8. Intimal thickening of aorta due to endothelial proliferation. (Rat)

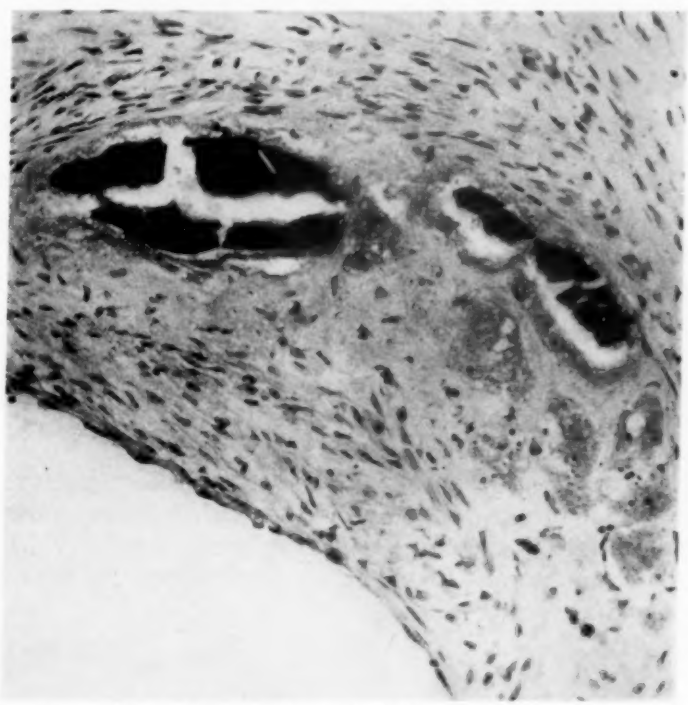

FIG. 9. Areas of fatty degeneration and calcification. Splenic artery of rat.

tion of the endothelial cells (figure 8). In the thickened area fine fibrils were seen producing a thickened subendothelial layer. The internal elastic lamina was, in several instances, frayed and split.

A medial degeneration with calcareous deposits was observed, associated with intimal changes, in some of the smaller arteries (figures 9 and 10). In many cases thrombosis had taken place in the atheromatous vessel (figure 10). In mesenteric vessels there was a very marked perivascular response —resembling quite closely periarteritis nodosa.

FIG. 10. Atheromatous plaque. Artery of rat.

Thus it is seen that in different species different arterial changes are produced by the same physiological mechanism. In the dog the lesions are chiefly medial, while in the rat intimal changes, with or without associated medial damage, are the prominent features. This is the case, of course, in the human type of arteriosclerosis.

The interpretation of progressive electrocardiographic records, the analysis of acute experimentation and the study of the microscopic sections of the animals used in these different experiments supply evidence to show the importance of a normal functional equilibrium between the two divisions of the autonomic nervous system.

Summary

1. Myocardial and coronary artery damage have been produced in dogs following chronic over-activity of the parasympathetic nervous system.

2. Gastric and duodenal congestion and ulceration have been produced by the same mechanism.

3. Similar lesions in the heart and in the gastrointestinal tract have been described in dogs dying of adrenal insufficiency.

4. Myocardial degeneration, atherosclerosis of the aorta and other vessels with or without associated arteriosclerosis have been produced in rats following chronic injections of the vagus substance—acetylcholine.

PNEUMOCOCCIC LOBAR PNEUMONIA: A REPORT OF 245 CASES WITH SPECIAL REFERENCE TO SPECIFIC SERUM THERAPY *

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It is our object in this report to present data accumulated between January 1935 and July 1937, in the treatment of lobar pneumonia, particularly with reference to specific serum therapy.

It has been our aim to examine carefully the results in the use of specific serum in suitable cases and to compare these results with those obtained in other cases in which, for some reason, serum was not used. We realize that the number of our cases is small compared to figures from larger institutions, but we wish to make our own modest contribution to indicate what good results can be obtained even in a hospital of moderate size. This hospital has four hundred beds and is one of two which serve a city with a population of about 150,000. Between January 1935 and July 1937, there were 3740 medical admissions, of which 245 cases were diagnosed lobar pneumonia—an incidence of 6.5 per cent.

In the past few years many contributions have been made to the study of lobar pneumonia and the use of specific serum treatment. We are deeply indebted to Cole [1] and his co-workers of Rockefeller Institute, to Cecil and Plummer [2] of Bellevue Hospital, to Sutliff and Finland [3] at the Thorndike Memorial Hospital and to others for their researches in this field. Although these workers have emphasized the successful results obtained with specific serum in pneumonias specifically typed, it appears that many medical men still hesitate to adopt this form of therapy in a disease which, even under the most favorable circumstances, must be regarded seriously.

According to the statistics [4] of the Metropolitan Life Insurance Company, pneumonia is still the third greatest cause of death. According to Cecil,[5] the combined average mortality of the pneumonias is close to 25 per cent. A short time ago, Benjamin [6] and his co-workers at the Cincinnati General Hospital pointed out several reasons why medical men are relatively slow in adopting serum therapy. They referred to the technical difficulties in sputum typing and commented on the fact that many practitioners still entertain some doubts of the efficacy of this treatment.

Cecil [7] and others in their reports stated that within the last decade, the curative value of specific serum has been definitely established in Types I and II, and that evidence is being accumulated to show that specific serum is also efficacious in Types V, VII, VIII and XIV. They, too, deplored the fact that the use of specific serum has not become more general, and mentioned as reasons the lack of facilities for typing pneumococci, the high

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From the Laboratory of the Bridgeport Hospital.

cost of the serum and hesitancy of the general practitioner to use it intravenously.

Gradually in the past few years, more and more laboratories have developed facilities for typing sputum. New York and Massachusetts have long since equipped their central and branch laboratories. Connecticut keeps its physicians advised of such laboratories available for their use. The high cost of serum still remains an important factor in preventing the general adoption of this procedure and the problem of distributing this burden must still be worked out. As to doubts in the minds of physicians of the efficacy of the treatment and their hesitancy in adopting it—these factors can only be obviated by familiarity with the statistics emanating from the great medical centers. These skeptical medical men will be won over only as more and more experience is accumulated and reported in the literature. More recent reports have unanimously indicated that the most valuable and at times the one life-saving procedure is the early use of adequate, specific serum in the treatment of lobar pneumonia.

It must be realized that our progress in the therapy of pneumonia is almost entirely due to reports coming from medical centers and large city hospitals. At these institutions the number of cases, the facilities for research and for compiling statistics are far greater than at smaller hospitals. The analysis, which we have made from our results, has been necessarily restricted due to the small number of cases and limited technical assistance. It is all the more interesting to note that with our limitations we have obtained such highly satisfactory results. This should be a stimulus to other institutions of similar size to consider specific serum therapy in all suitable cases.

First, let us define the condition for which we recommend it. We consider lobar pneumonia as an acute inflammation, involving one or more lobes of the lung, produced by some strain of pneumococcus. Since the prognosis and the treatment depend so much on the specificity of the bacterial agent, we have placed particular stress not only on identifying the inciting organism but also on the technic of typing-out the specific strain of pneumococcus. Great progress has been made since Neufeld and Händel in 1909 working in Germany and Dochez and Gillespie in the United States in 1913 showed that all pneumococci were not alike and that the different types could be identified and differentiated. Gradually more and more strains of pneumococci have been separated serologically so that now there are 32 distinct types. Due to the limited size of our laboratory staff and to the fact that up to the time this paper was written there were available but a few specific sera for therapy, we in the laboratory have typed out only the following strains: Types I, II, III, IV, V, VI, VII, VIII and XIV. Other pneumococci were identified and reported only as belonging in certain polyvalent mixtures which corresponded to those found in the commercial diagnostic sera sets. We are planning to go further and type out specifi-

cally each of the 32 types of pneumococci as the commercial specific sera become available for each.

The basis of this study is 245 cases of lobar pneumonia caused by pneumococci. Our criteria in making the diagnosis of pneumococcus lobar pneumonia were: Sudden onset, a chill and fever, pain in the chest and cough with rusty sputum which, on typing, showed pneumococci. In each case the above findings were corroborated by physical examination showing lobar consolidation. In the presence of doubtful physical findings, roentgen-ray examination showed consolidation. Of the 245 cases there were 166 adults and 79 children. Table 1 shows the incidence of males and females, of adults and children, and the mortality as found in our entire series.

It is seen that the incidence among males was slightly less than twice as high as among females but the mortality among the males was 2.5 times that of females. The mortality in the adult group was 14.4 per cent. Painton [8] found an incidence of males to females in the ratio of 3 to 1 with 10 per cent higher mortality among the males. The greater incidence among

TABLE I

Incidence and Mortality According to Sex

	No. Cases	% Incidence	No. Deaths	% Mortality	% Mortality
Adults					
Male	109	44.5	17	15.7	14.4
Female	57	23.2	7	12.3	
Children under 12 years					
Male	48	19.6	0	0	1.2
Female	31	12.7	1	3.2	
Total	245		25	10.2	

males is probably due to their occupations, living conditions and habits, including the greater use of alcohol.

Table 2 shows the incidence of pneumonia cases as distributed among the age groups and sexes as indicated. There were 79 children under the age of 11 years in our series—an incidence of 32.2 per cent with only one death or 1.2 per cent mortality. This was a female, four years of age, seen for the first time on the eleventh day of her illness, having an unclassified type of pneumococcus pneumonia with empyema. She died three days after admission and postmortem findings confirmed the diagnosis. When we consider the entire series it is apparent that 80 per cent of all pneumonia cases seen at this hospital were in persons under the age of 50 years. It is well known that age is an important factor in the mortality. Between the ages of 41 and 60, the mortality rate was 18.5 per cent, while beyond 60 the mortality rose to 46 per cent. The single decade showing the highest incidence among adults was between 41 and 50 years, while the single decade showing the highest mortality was between 71 and 80 years.

As a matter of interest, we have compared the relative incidence of individual and multi-lobar involvement on the right and left sides. Right sided involvement was 1.5 times more frequent than the left sided involvement, as seen in table 3. The mortality in right lung involvement was 2.5 times as high as when the left lung was involved.

TABLE II

Incidence and Mortality among Age Groups

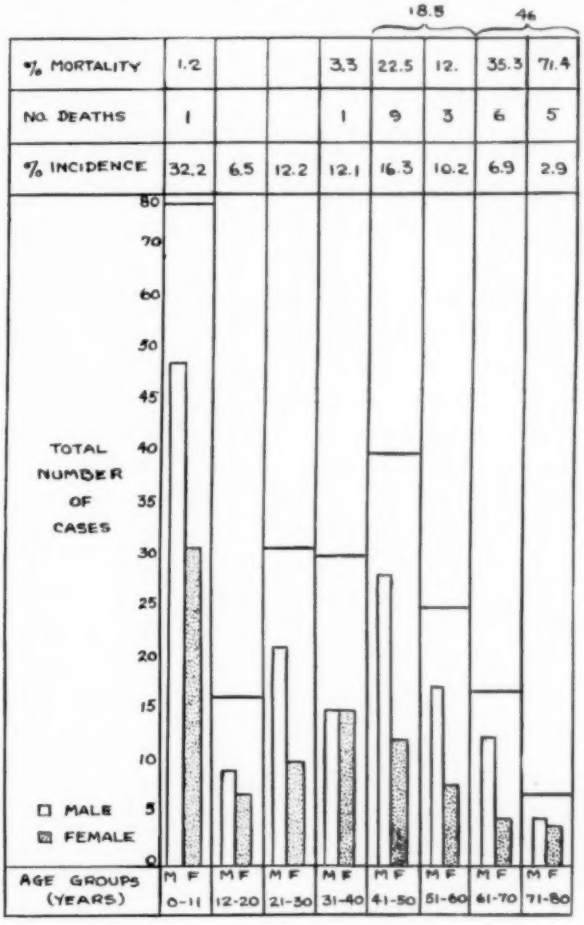

TABLE III

Incidence of Lobe Involvement

Lobe	No. Cases	% Incidence	No. Deaths	% Mortality
R. U. L.	37	15.1	4	72
R. M. L.	24	9.8		
R. L. L.	96	39.0	14	
L. U. L.	11	4.	1	28
L. L. L.	100	40.8	6	

Table 4 shows the incidence and mortality of the pneumonias according to the serological types. It is noted that Type I pneumonia occurred in 104 or 42.5 per cent of all the cases studied.

Typical lobar pneumonia cases, in which the inciting organism was not serologically identified as to type because of our limited facilities, numbered 54 or 22 per cent of the total. Up to the time of writing, there are no available sera for members of this unclassified group. In this table we note that the mortality in the Type I pneumonias, for the combined serum-treated and non-serum-treated cases, is 4.8 per cent; compared to the crude mortality for the entire series, which is 10.2 per cent. It has been shown by many extensive reports that specific serum reduced the mortality in Type I pneumonia. As more evidence is accumulated in the specific treatment of the other types for which there is available serum, we feel that there will be an appreciable reduction in the morbidity and mortality in those types as well.

In the review of this series of cases we found no standard or routine

TABLE IV

Incidence and Mortality among Serological Types

Type	No. Cases	% Incidence Cases	No. Deaths	% Mortality
I	104	42.5	5	4.8
II	3	1.2	0	
III	10	4.1	3	30.
IV	13	5.3	2	15.
V	14	5.7	2	14.3
VI	4	1.6	0	
VII	15	6.1	0	
VIII	22	9.0	2	9.1
XIV	6	2.4	0	
Unclassified	54	22.0	11	20.4
Total	245		25	10.2

dosage of serum, since the cases were selected from the services of several physicians and the series included both general and private cases. However, it was noted that 54 cases of Type I pneumonia, or 64.3 per cent, were given doses varying between 40,000 and 100,000 units. The writer has adopted the plan of giving the patient an initial dose of 100,000 units of serum as soon as careful skin and eye tests were found negative. If the temperature did not fall in four hours, another 60,000 units was given. We feel that large doses of serum given at the earliest moment after careful typing and serum-sensitivity tests have been completed, will produce the best results.

In table 5 there is presented the serum-treated and non-serum-treated cases according to the various types of pneumococci found.

There were 120 cases treated with specific serum with four deaths—a mortality of 3.3 per cent. In the non-serum-treated cases, which numbered 125, there were 21 deaths or 16.8 per cent mortality. The unclassified

TABLE V

Comparison of Mortality between Serum- and Non-Serum-Treated Cases

Pneumococcus Type	Total No.	Serum Cases			Non-Serum Cases		
		No.	Deaths	% Mortality	No.	Deaths	% Mortality
I	104	84	3	3.6	20	2	10.
II	3	3					
III	10				10	3	30.
IV	13				13	2	15.
V	14	8	1	12.5	6	1	16.6
VI	4				4		
VII	15	11			4		
VIII	22	11			11	2	18.2
XIV	6	3			3		
Unclassified	54				54	11	20.4
Total	254	120	4	3.3	125	21	16.8

type of pneumonias showed 11 deaths or a mortality of 20.4 per cent. Of the 104 Type I pneumonias, 84 cases or 80.8 per cent were given specific serum. There were three deaths in this group—a mortality of 3.6 per cent. Two of these three patients who died, came into the hospital on the third and seventh days of their illnesses, respectively, both were alcoholics in delirium tremens and both died within 24 hours. The third patient was a woman seen on the seventh day, who died within 24 hours after admission. In the Type I non-serum-treated group, there were 20 cases with two deaths or a mortality of 10 per cent. One of these patients was a male, seen on the third day with a positive blood culture who, for some reason, did not receive any serum. He died within 24 hours. The other patient was a female, age 75 years, a chronic alcoholic, who died within 24 hours and post mortem showed consolidation of the left lower lobe and right middle and lower lobes with empyema and pericarditis. Grouping all the Type I patients, the five deaths gave a mortality rate of 4.8 per cent but all five were in extremis when admitted and died within 24 hours.

When we compare the mortality of 16.8 per cent in the non-serum-treated cases with the mortality of 3.3 per cent in the serum-treated cases and 3.6 per cent in the serum-treated Type I cases, we note that the reduction in the mortality is most striking. In addition, when Type I cases were treated with serum, there was noted a marked reduction in the morbidity of the patients.

Table 6 shows the distribution of the various types according to the day of illness when first seen. Seventy-eight cases of Type I pneumonia, or 75 per cent, were seen in the first four days, when the administration of serum is likely to be most effective. Clinically, these patients showed marked improvement within a few hours after the serum was given. In the

TABLE VI

Distribution of Various Types According to Day of Illness on Admission to Hospital

Day of Illness Patient Admitted	Type I	II	III	IV	V	VI	VII	VIII	XIV	Unclassified	Total
1	2	1		1			1	2			7
2	41	2	4	3	4	1	3	4	5	9	76
3 75%	25		3	3	2	3	7	6		12	61
4	10			2	2		1	6		8	29
5	11		3		2		1			13	30
6	3							2		2	7
7	9			3	4		3	1	1	7	28
8	1										1
9	2										2
10				1						1	2
11								1		2	3

173 or 70.6 %

majority of cases, the temperature soon began to fall. In 46.4 per cent of the cases the patients had a crisis and the temperature reached normal within 24 hours. In 72.6 per cent of the cases it reached normal within 48 hours. The pulse rate dropped within normal range, respirations became slower and easier and the general condition was greatly improved. Many times the change in the clinical picture from that of a severely ill person to one who sat up in bed within a few hours after receiving serum, seemed miraculous. In the non-serum-treated cases only two had a crisis within 48 hours, the other 16 cases terminating by lysis. In the cases treated with specific serum, other than Type I, there were 17 cases or 54.8 per cent that showed a crisis within 48 hours while in the non-serum-treated cases other than Type I only 2.3 per cent terminated by crisis. Although our series is small, there is no doubt in our minds that the administration of serum precipitates the crisis in about three-fourths of the cases, with a concomitant amelioration of symptoms.

As to the use of specific serum in pneumonia other than Type I, the number of our cases is too small to permit any conclusions. In comparison to the reports of other observers, the incidence of Type II pneumococcus pneumonia in this series was surprisingly small. For some reason only three Type II pneumococcus pneumonias were noted. All of these were given serum and had prompt crisis with recovery.

In Type V cases, which numbered 14, eight were given serum. One patient was seen on the seventh day of his illness. He had a positive blood culture and although given 280,000 units of serum, he died nine days after admission. At post mortem there was found a resolving pneumonic consolidation of the right upper and middle lobes with a purulent mediastinitis. The other fatal Type V case received no serum. He was seen on the seventh day, died three days later and at post mortem showed consolidation of the right upper and lower lobes.

There were 15 Type VII cases, 11 of which received serum and four did not. They all recovered but the clinical course of those receiving serum was much milder and the hospitalization of the serum-treated cases averaged 11.2 days, while in the non-serum-treated cases hospitalization averaged 22 days.

Of the Type VIII cases, there were 22, of which 11 were given serum and 11 were not. In the serum-treated cases, hospitalization averaged 14.7 days, while in the non-serum-treated cases hospitalization averaged 17.4 days. In the latter group, two died—a mortality of 18.2 per cent. Both of these fatal cases were seen on the seventh day, one of them a pregnant woman who aborted during her illness and died five days after admission and at post mortem showed empyema in the right chest.

There were only six cases of Type XIV, three of which were given serum and three were not. All recovered and the entire number of cases is too small to comment upon.

Table 7 shows the incidence of complications. Empyema developed in 17 instances (6.9 per cent). It is interesting to note that nine of these

TABLE VII

Incidence of Complications

Complication	No. Cases	% Incidence
Empyema	17	6.9
Otitis Media	5	2.1
Pleural Effusion	2	0.8
Pericarditis	1	0.4
Mediastinitis	1	0.4
Total	26	10.6

empyema cases occurred in Type I pneumonias which were given serum and two in Type I which were not given serum. The other six empyema cases were distributed among the other types. Of all the fatal cases, empyema was found in only three—one in a Type I non-serum-treated case and two in the unclassified group.

COMMENTS ON SERUM THERAPY

We realize that the total number of serum-treated cases—120 in our series, is small compared to reports from larger institutions. According to the most recent statistics [9] in the *Journal of the American Medical Association,* out of 712 accredited hospitals throughout the United States, there are 582 hospitals having 400 beds or less. Our hospital has only 400 beds but it is apparent that hospitals of this size or smaller form 81.7 per cent of the hospitals in this country. In view of this fact, our results are interesting and instructive.

Since there is no method to determine in advance the minimum effective

dose of serum in any case, we believe that a relatively large dose of 100,000 units should be given at once, after specific typing and serum sensitivity tests have been done. In no case where the cutaneous and ophthalmic tests were negative have we seen any harmful serum reactions, no matter how much serum was given at one dose. This is probably due to the quality of the concentrated and highly purified serum that was used. In all of the 120 serum-treated cases, only 12 cases of serum sickness developed—an incidence of 10 per cent.

Our observations have convinced us that if sufficient serum be given within the first four days, it is possible in the great majority of cases to cut short the course of pneumonia and bring about an earlier recovery than would otherwise take place. Although it is true that the effectiveness of serum is apparently greater the earlier in the disease it is given, our experience indicates that every patient, however late he is seen, should receive it.

In evaluating the effect of specific serum, we consider its effect on the morbidity and mortality. In practically all the favorable cases the temperature fell and symptoms were rapidly ameliorated. The mortality was strikingly lower in the serum-treated cases, being 3.3 per cent, compared to 16.8 per cent in the non-serum-treated cases. These results compare favorably with those reported from the larger institutions.

Although the duration of hospitalization of pneumonia patients varied with the physician and the class of service, it was certain that the hospital stay of those patients treated with serum was much shorter than in the non-serum-treated cases. Without doubt, the greatest reduction in mortality was in the Type I infections. Although our experience with specific serum in the other types was limited, we observed a definite lowering of the mortality in the serum treated cases of the Types V, VII, VIII and XIV. The mortality in this group of serum-treated cases was 3 per cent as compared to 12.5 per cent in the non-serum-treated cases. In our series, 67 per cent of all lobar pneumonias fell into types for which there is available specific serum. This compares with 65 per cent as found by other observers.[6] We feel that none of these patients with types of pneumonia for which there is available specific serum should be deprived of the benefits of this therapy.

The difficulty of providing specific serum because of the high cost is gradually being met by the proper authorities. Increased use, as well as improvement in the methods of manufacture and distribution, have combined to reduce the expense involved. For those who cannot afford to pay the entire cost some other provision must be made, such as state aid, so that even the indigent patient may receive serum when he requires it.

Summary and Conclusions

1. In a two and one-half year period, 245 cases of lobar pneumonia were studied. Of these 164, or 67 per cent, fell within the Types I, II, V, VII, VIII and XIV, for each of which there is available specific serum.

2. Type I cases numbered 104, of which 84 were treated with serum with a mortality of 3.6 per cent. This was in contrast to the death rate of 10 per cent in untreated Type I cases.

3. In a much smaller number of cases consisting of Types V, VII, VIII and XIV which were treated with specific serum the mortality was 3 per cent compared to 12.5 per cent in the non-serum-treated cases.

4. In a total of 120 serum treated cases, the death rate was 3.3 per cent while in the 125 non-serum-treated cases the mortality was 16.8 per cent.

5. Serum sickness was observed in only 12 cases. Skin and eye tests for sensitivity can reduce serious serum complications to a negligible minimum.

6. From our experience, therefore, Type I serum should be given as early as possible and in large amounts, no matter how late the patient is seen.

7. As for the other specific types for which therapeutic serum is available, our experience indicates that all patients having pneumonia of the types for which therapeutic serum is available, should be given the benefits of specific serum therapy.

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URINARY DIASTASE IN ACUTE PANCREATIC NECROSIS: AN EXPERIMENTAL INVESTIGATION *

By C. J. Smyth, M.D., *Ann Arbor, Michigan*

Until recently, acute pancreatic necrosis has been considered a surgical emergency and universally regarded as an indication for immediate operation. At present the trend is toward more conservative treatment. Trasoff and Scarf [1] have reviewed this problem and analyzed the records of 16 patients with acute pancreatitis. Three of the four subjected to early operation died, whereas of 12 not operated upon, 9 recovered. Hartlieb [2] is opposed to surgical intervention, and has treated 9 patients expectantly, of whom 7 recovered. Mikkelsen [3] reported 39 examples of acute pancreatitis, all of which were treated conservatively with a mortality of only 7.5 per cent.

If operation is to be deferred as these and other observers advocate, it becomes increasingly important for the physician to be certain that he is dealing with this disease and not with some other abdominal emergency in which delay might be fatal. Various observers (Nordmann,[4] Rost,[5] Foged,[6] McCaughan [7]) indicate that with the aid of laboratory tests for diastase it is possible to establish a preoperative diagnosis of acute hemorrhagic pancreatitis in about 85 per cent of cases. Mushin [8] has reported a gratifying improvement in preoperative diagnostic accuracy since this test has been introduced. When it was not used in doubtful upper abdominal crises the condition was diagnosed prior to operation in only 30 per cent of cases. Following its use, when the urinary diastase has been elevated, operation has confirmed the provisional diagnosis. Equally favorable is the report of Foged,[6] who studied the diastase reaction of the urines of 71 patients with acute pancreatitis. In 70 per cent there was a significant increase in the diastase. Where no test has been employed the preoperative diagnosis is unsatisfactory. Schmeiden and Sebening,[9] in a review of 2,137 cases from various German clinics, found a correct diagnosis in only 21.8 per cent. Colp,[10] in 1930, surveyed 54 cases and of these only 30 per cent were correctly diagnosed before operation. Abell [11] reports a slightly higher percentage, 12 of 30 cases, or 40 per cent.

Diastase was first isolated from the urine by J. Cohnheim in 1863. Its exact origin is not known but most of it appears to be liberated by the pancreatic acini. Extra-pancreatic sources exist, for it is found in the blood after total pancreatectomy. Wohlgemuth,[12] in 1908, introduced a practical quantitative method for its determination and a modification of his original method is the basis of the most commonly employed test today. In principle it is based upon the hydrolysis of starch to maltose, erythro-

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dextrin or achroödextrin by diastase, the result depending upon the concentration of the enzyme, and testing by the addition of iodine. Wohlgemuth's "diastase unit" is the amount of ferment contained in 1 c.c. of urine which at 38° C. and in 30 minutes is able to break down 1 c.c. of 0.1 per cent starch.

In the estimation of diastase in urine, we have used a modification of the Wohlgemuth test. One cubic centimeter of recently voided urine is placed in the first and second of a series of 13 test tubes. To all tubes except the first, 1 c.c. of 1 per cent salt solution is added. The contents of tube two (1 c.c. of urine and 1 c.c. of salt solution) are mixed with a pipet and 1 c.c. of this mixture is placed in the third tube. This procedure is repeated through the series, resulting in dilutions of urine of ½, ¼, ⅛, 1/16, 1/32, etc., to 1/4096. To each test tube is then added 2 c.c. of 0.1 per cent starch solution. All of the tubes are then placed in a water bath at 38° to 40° C. for 30 minutes. At the end of this time the tubes are cooled to retard hydrolysis and a saturated aqueous solution of iodine is added drop by drop. The iodine causes the appearance of yellow, reddish brown, bluish red or blue in the various tubes. The tube showing the first appearance of the color blue is taken as the end point and the calculation of the diastase value is made from the tube immediately before it. Thus if the fifth tube is the first to show the blue color, the dilution in the fourth tube is used to determine the diastase units: $\frac{2 \text{ c.c. (of starch)}}{\frac{1}{8} \text{ (dilution of urine)}} = 16$. By this method diastase values up to 8192 can be determined.

Many diastase determinations have been made on normal individuals and on patients with various illnesses. Values between 4 and 32 units are considered normal. Foged,[6] who has studied the urine diastase in over 4,000 patients, considers only amounts higher than 300 units definitely pathological. In 59 of the 71 cases of acute pancreatic necrosis which he studied, values of 1200 or more were recorded. Beigler and Marcus,[13] who have employed the Wohlgemuth method, examined 237 patients with various abdominal conditions. In this group there were 15 with acute pancreatic necrosis and in these, diastase values were always between 320 and 2000 units. Rost[5] also has reported uniformly high urine diastase values in this disease. In 10 of his 13 patients, between 1000 and 8000 units were present; and in 2, between 128 and 258 units. In Mushin's[8] series of 26 cases the diastase value ranged between 50 and 4100 units. From the literature it may be concluded that in acute pancreatic necrosis there is a prompt elevation in the diastase values beginning six to eight hours after the onset of the disease. Following this rapid rise there is a return to normal, usually by the end of the third day. Therefore, to be of any value, the urine must be tested during the first three days. Even by the end of 36 hours, the diastase value may have fallen to normal.

Among the other pathological conditions which have been observed to cause an elevation in urine diastase, common-duct stone is the most frequent. Values over 300 were recorded in 61 per cent of a series of 69 patients with common-duct stone studied by Foged.[6] This observer considers an elevated diastase value as the surest of all laboratory procedures when confronted with a differential diagnosis between hepatitis, cancer of the pancreas, and common-duct stone. However, a stone lodged in the common-duct does not necessarily bring about an elevated diastase. Severe acute cholecystitis has been noted on several occasions to give an abnormal reading. All observers stress that this test, as any other laboratory procedure, must be considered only an adjunct to the clinical picture and history. There is agreement that, although increased values may occur in other acute abdominal conditions, a normal finding excludes a pathologic process located in the pancreas.

In the course of an experimental investigation of the pathogenesis of acute pancreatic necrosis, opportunity was afforded to test the validity of the urinary diastase reaction on carefully controlled material. (The tissue lesions produced will be reported elsewhere.)

Acute pancreatic necrosis has been produced in dogs by the injection, under surgical technic, of small droplets of metallic mercury into one of the

TABLE I

Urinary Diastase Determinations Following Experimental Pancreatic Infarction

	Dog No.	Number of Diastase Determinations	Highest Diastase Value	Series Considered Satisfactory	Remarks
Food as Pancreatic Stimulus	VI	22	64 units	Yes	Chronic interstitial pancreatitis.
	VII	19	256 units	Yes	Pancreatic abscess.
	VIII	9	128 units	No	Acute pancreatic necrosis. Perforation of duodenum. Generalized peritonitis. Lived only 22 hours.
	IX	4	16 units	No	Died within 2 hours.
	X	1	8 units	No	Acute pancreatic necrosis. Death 22 hours post-operative. Duodenal perforation.
	XI	2	4 units	No	Died within 2 hours.
	XII	18	1024 units	Yes	Pancreatic abscess.
	XIII	14	256 units	Yes	Acute pancreatic necrosis.
	XIV	17	32 units	Yes	Small abscess of pancreas.
	XV	11	2 units	Yes	Small abscess of pancreas.
Acetyl-β-Methyl-Choline Chloride and Physostigmine	XVI	15	32 units	Yes	Small chronic pancreatic abscess.
	XVII	17	256 units	Yes	Pancreatic abscess.
	XVIII	10	1024 units	No	Acute pancreatic necrosis. Perforation of duodenum. Generalized peritonitis. Death 26 hours post-operative.
	XIX	8	128 units	Yes	Acute pancreatic necrosis. Small abscess.
	XX	11	128 units	Yes	Chronic interstitial pancreatitis.
	XXI	13	8192 units	Yes	Subacute hemorrhagic pancreatitis.

pancreatic arteries at a time when the pancreas was stimulated to the height of its secretory activity. Sixteen animals were used, divided into two groups. In one series of 10, food was used as a stimulus by giving a meal of meat and cereal two hours before operation. In a second group of six dogs, subcutaneous injections of acetyl-β-methylcholine chloride, in doses of 0.5 mg. per kilo of body weight, together with 1 mg. of physostigmine salicylate, were given. Friedman and Thompson [14] have shown that these drugs given together are powerful stimulants to pancreatic secretory activity.

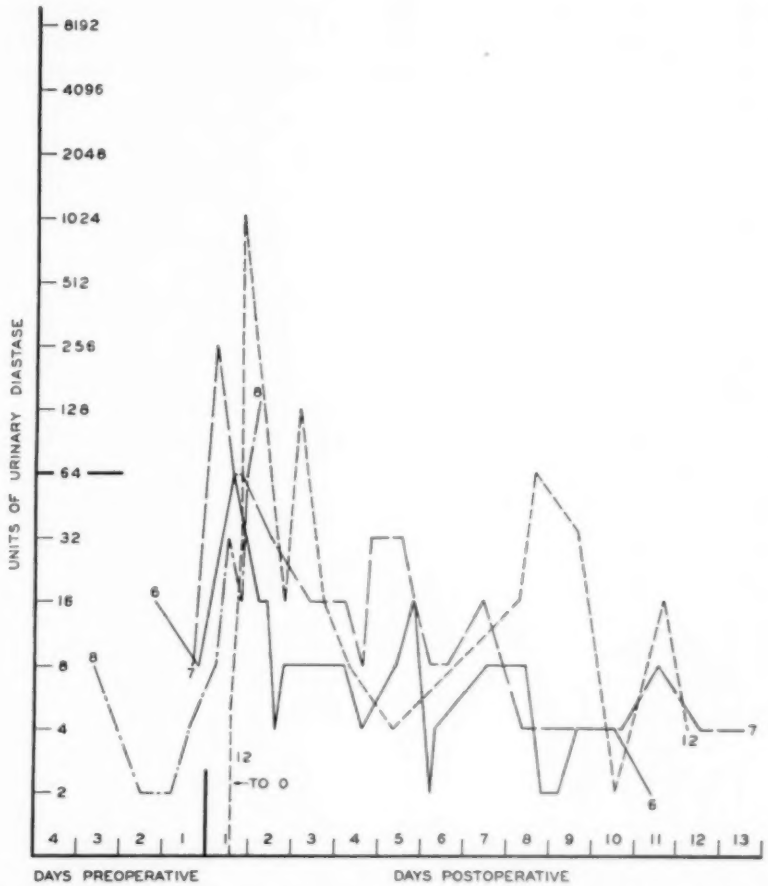

FIG. 1. Variations in urine diastase units in four selected dogs fed before operation at which pancreatic infarcts were experimentally produced. Each line refers to the animal designated by number.

Daily preoperative and frequent postoperative urine diastase tests were made by the method described above, with a total of 119 determinations. The results appear in table 1.

Opportunity for a satisfactory series of diastase studies was present in 11 of the 16 dogs. Of the five remaining animals, two (IX and XI) failed

to recover from the anesthesia and died within two hours after the operation. The other three (VIII, X and XVIII) died within 26 hours after the operation from generalized peritonitis resulting from perforation of infarcted areas in the duodenum.

Urine diastase values in 8 of the 11 animals in which an adequate number of specimens were examined were significantly elevated. Figures 1 and 2 illustrate these variations in those cases where elevated diastase

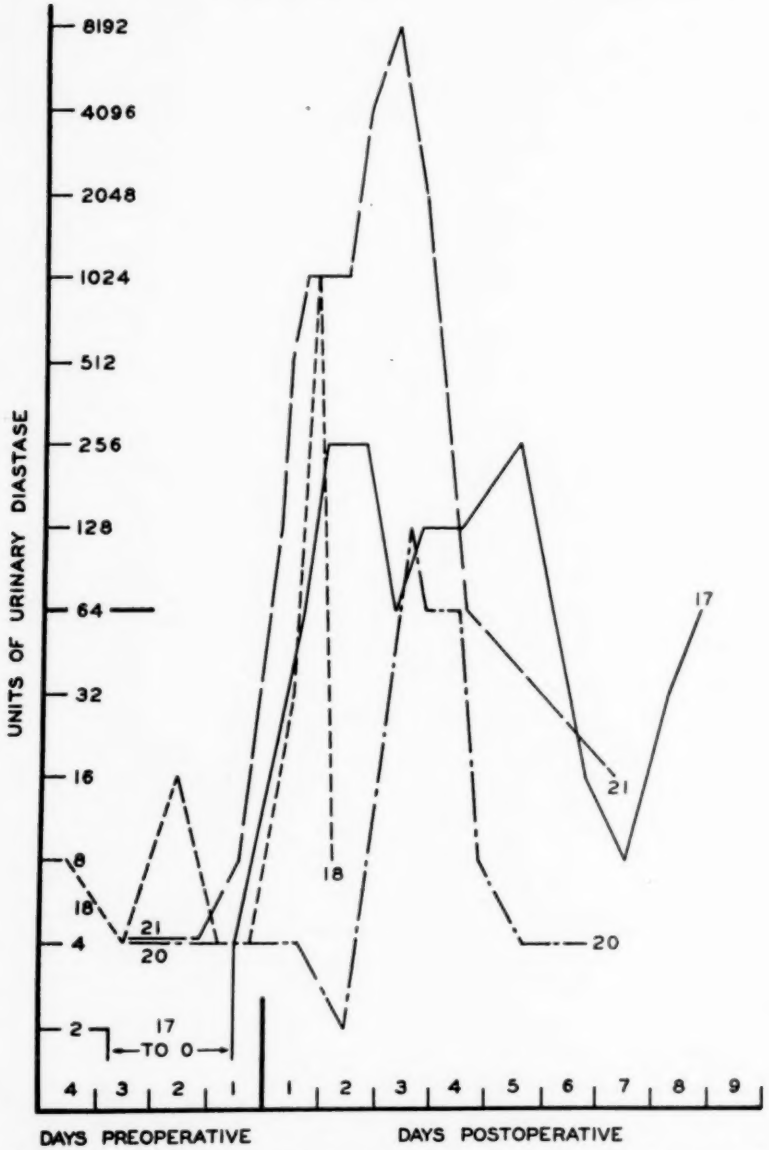

FIG. 2. Variations in urine diastase in four selected animals injected with acetyl-β-methylcholine and physostigmine before production of pancreatic infarcts.

values were recorded. Postmortem examinations were made immediately after death and in all cases there were either gross or microscopic evidences of pancreatic necrosis. The areas of pancreatic necrosis produced by this embolic method did not extend to non-infarcted adjacent tissue. In the first group the dogs were sacrificed between the eleventh and the fifteenth day, and in the second group between the fifth and ninth day following operation.

These studies indicate that the urinary diastase test is a useful index to the presence of acute pancreatic necrosis. The viscosimetric methods used in studying blood diastase are more accurate. However, since the modified Wohlgemuth method requires very little apparatus, the reagents are easily prepared, and the time required is only 45 minutes, its more frequent use is recommended.

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THE EFFECT AND RATE OF REMOVAL OF PYRUVIC ACID ADMINISTERED TO NORMAL PERSONS AND TO PATIENTS WITH AND WITHOUT "VITAMIN B DEFICIENCY"*

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Pyruvic acid has long been known as an intermediary product of carbohydrate metabolism. Nevertheless, there are but few reports on the pharmacological action of this substance in higher animals [1, 2] and, so far as we know, none on its action in human beings. Recently, considerable importance has been attached to pyruvic acid, chiefly through the rôle claimed for it in vitamin B_1 deficiencies. Peters and his coworkers [3] consider it an important, if not a specific substance in the "biochemical lesion" in experimental B_1 deficiency states, while Platt and Lu [4] report increased amounts of pyruvic acid in the blood, spinal fluid and urine of patients with "wet" beriberi. The work of these authors suggested the possibility that the lack of B_1 in the organism may disturb the normal metabolic pattern and result in the accumulation of abnormal intermediary metabolites, particularly of pyruvic acid, which in turn may produce the clinical symptoms and signs of vitamin deficiency.

Sherman and Elvehjem,[5] on the other hand, were unable to find increased amounts of bisulphite binding substances (including pyruvic acid) in the blood of B_1 avitaminotic chicks, although they did find increased amounts in the cloacal contents. They claim, however, that sodium pyruvate, when injected intravenously into these deficient birds, causes a prolonged rise in the blood bisulphite binding substances (B.B.S.), while in normal birds it causes no rise even immediately after injection. They conclude, therefore, that deficient birds are incapable of adequately removing pyruvic acid from the circulating blood and postulate that the defect lies in the intrinsic metabolism. De Jong [6] also has studied the B.B.S. of the blood of pigeons with B_1 deficiency. He found that polyneuritis usually developed before the rise of the B.B.S and that the symptoms often disappeared while the B.B.S. remained elevated. Chronic polyneuritis was not associated with a rise in the B.B.S.

For the past two years an investigation has been in progress in this laboratory on the physiological and biochemical nature of the disturbances associated with vitamin B (B_1) deficiencies in human beings and in rats.[7, 8, 9, 10, 11, 12] The present study of the pharmacology of pyruvic acid in normal and in diseased human subjects was undertaken in order (1) to determine

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the effect, the rate of removal and the excretion of sodium pyruvate injected intravenously in (*a*) normal subjects and (*b*) patients with various diseases, particularly vitamin B_1 deficiency; (2) to determine the absorption, action and excretion of sodium pyruvate administered orally; (3) to correlate, if possible, the pharmacological action of sodium pyruvate administered in single large doses with functional disturbances of vitamin B_1 deficiencies in human beings; and (4) to ascertain whether differences exist in the rate of removal of sodium pyruvate from the blood of normal human beings and of human beings with B_1 deficiency, similar to those reported in chicks by Sherman and Elvehjem.

Procedure

Pyruvic acid * was neutralized with sodium hydroxide to pH 7.4, diluted with distilled water to make solutions containing 5 and 10 per cent pyruvic acid by volume, and again adjusted to pH 7.4. For intravenous use the 5 per cent solution was sterilized by passage through a Berkefeld filter. For oral use the 5 or 10 per cent solution was diluted just before administration with one-half volume of tomato juice in order to disguise the taste.

Subjects were studied in the fasting state and had been at rest for at least 30 minutes before observations were begun. The heart rate was counted by arterial palpation, by precordial auscultation or from the electrocardiogram; the arterial pressure was measured by arterial auscultation, using a mercury manometer; and electrocardiograms were taken with a string galvanometer, using the three standard leads and the cardiac apex lead. The rate and depth of respiration were noted, the tendon reflexes were tested, and signs and symptoms were searched for throughout the experiment. After control conditions were established blood and urine samples were obtained for chemical studies.

After numerous cautious trials it was decided to use for intravenous administration 100 ml. of 5 per cent sodium pyruvate, infused by gravity into the median cubital vein, allowing 3½ minutes for the injection. The amount and rate of injection were the same in all cases without regard to the body weight or to the state of the circulation. Immediately after the pyruvate had run in, a venous blood sample was taken from the opposite arm, the heart rate and arterial pressure were determined and an electrocardiogram was taken. Similar observations were made and blood samples were taken 5, 15, 30 and 60 minutes after injection. Urine samples were obtained as soon as possible following injection and every one or two hours thereafter.

In the experiments with oral administration the solution was taken in one dose. The heart rate and arterial pressure were determined at 10-minute intervals, and electrocardiograms and venous blood and urine samples taken at varying intervals, according to the changes expected.

* Eastman Kodak Company "Research Grade."

Blood samples were analyzed for content of non-protein nitrogen and of glucose by the methods of Folin,[13] and for carbon dioxide capacity by the method of Van Slyke.[14] Pyruvic acid was determined indirectly by means of the bisulphite binding substances (B.B.S.), using a modification [10] of the method of Clift and Cook.[15] The increases in B.B.S. found after administration of pyruvate were interpreted as due to pyruvate.

Urine samples were measured and analyzed for acidity, sugar, acetone and diacetic acid by the routine methods, and for pyruvic acid by a modification [16] of the Simon-Piaux method.[17] In order to obtain the urine specimens during the experiments, subjects were given as much water as they would tolerate. Samples were collected until pyruvic acid had disappeared.

The electrocardiograms were examined and measured with particular attention to the duration of electrical systole, which was calculated by the formula, $K = \frac{Q-T}{\sqrt{R-R}}$.[18]

Subjects

Nine subjects were normal adults. Six received 100 ml. of 5 per cent sodium pyruvate intravenously, two received 100 ml. of 5 per cent pyruvate by mouth and three received 250 ml. of 10 per cent pyruvate by mouth.

Of 12 patients, six had no clinical evidence of vitamin B deficiency. Three of these had organic heart disease with varying degrees of congestive failure; two had liver disease with jaundice and one had severe diabetes mellitus, which was fairly well controlled with insulin. Five patients suffered with probable vitamin B_1 deficiency, varying in degree from severe "wet" (cardiovascular) beriberi to mild polyneuritis. There was one case of pellagra without neuritis.

All patients received the pyruvate intravenously and some, in addition, received it by mouth. In the "vitamin B deficient" patients, whenever possible the procedures were performed both before and after specific treatment in the form of crystalline vitamin B_1.

Results

A. Intravenous Injection of 100 ml. of 5 Per Cent Sodium Pyruvate

1. *Normal Subjects.* Table 1 summarizes the results of the six experiments on the normal group. Chart 1 shows graphically the results of a typical experiment, while chart 2A shows the blood B.B.S. curves for all experiments. It will be seen that there was essentially no effect on the heart rate or the blood pressure. Neither was there any noticeable change in respiratory rate or depth, or in the tendon reflexes. No symptoms were elicited except those that could be attributed to mild anxiety and excitement caused by the procedure, and occasionally a slight sensation of generalized "prickling" immediately after the injection, probably due to rapid infusion

TABLE I

NORMAL SUBJECTS:

Intravenous Infusion 100 ml. 5 Per Cent Sodium Pyruvate

Subject No.	Blood B.B.S. (mg./100 ml.)				Blood Sugar (mg./100 ml.)			Plasma CO_2 Capacity (vol. %)			Urine Pyruvic Acid	Electrocardiogram "K"	
	Initial Value	Change After Injection			Initial Value	Change After Injection		Initial Value	Change After Injection		No. Hrs. Positive	Change	Time of Change (min.)
		Immediately	5 min.	1 hour		5 min.	1 hour		5 min.	1 hour			
1	5.25	+10.95	+6.17	+0.50	96.6	+5.8	+1.4	54.5	+4.3	−1.4	6	+0.02	8
2	3.96	+ 9.64	+9.14	+0.53	95.3	−2.5	−4.6	64.4	+0.8	−2.2	5	+0.03	2
3	3.75	+11.05	+8.75	+2.50	87.7	0	−1.5	63.0	+1.9	−1.7	4	+0.03	2
4	3.88	+12.39	+6.47	+0.52	99.7	−2.4	−9.4	67.4	+6.9	—	4½	+0.04	2
5	5.27	+ 8.53	+9.73	+2.76	100.5	0	+4.7	—	—	—	6½ +	+0.06	2
6	4.16	+17.44	+7.19	−0.34	not fasting	—	—	—	—	—	2 +	—	—

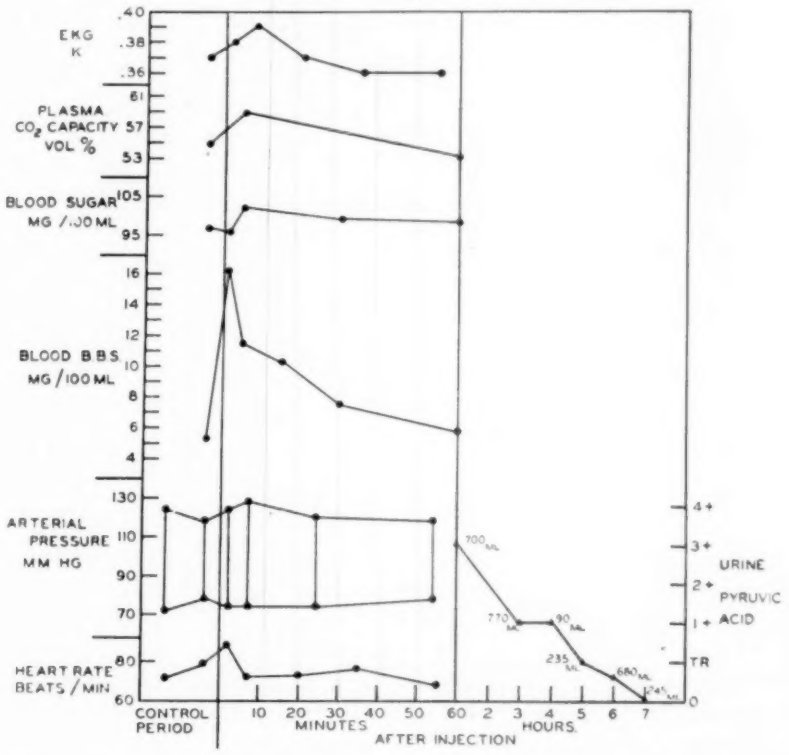

CHART 1. The effect of 100 ml. of 5 per cent sodium pyruvate, injected intravenously in a normal male subject, on the heart rate, arterial blood pressure, bisulphite binding substances (B.B.S.) in the blood, blood sugar, plasma carbon dioxide capacity, electrical systole of the heart (calculated as K), and pyruvic acid in the urine.

of the hypertonic solution. The B.B.S. rose sharply to a peak immediately after the injection, then decreased to practically its original level in the course of an hour. Pyruvic acid was found in the urine by qualitative test as early as 15 minutes after injection and for periods up to six hours, during the major part of which the B.B.S. level in the blood was essentially the same as during the control period. These results are interpreted to mean that sodium pyruvate is a low threshold substance for the human kidney, and that the qualitative test on the urine represents a fairly accurate gauge of

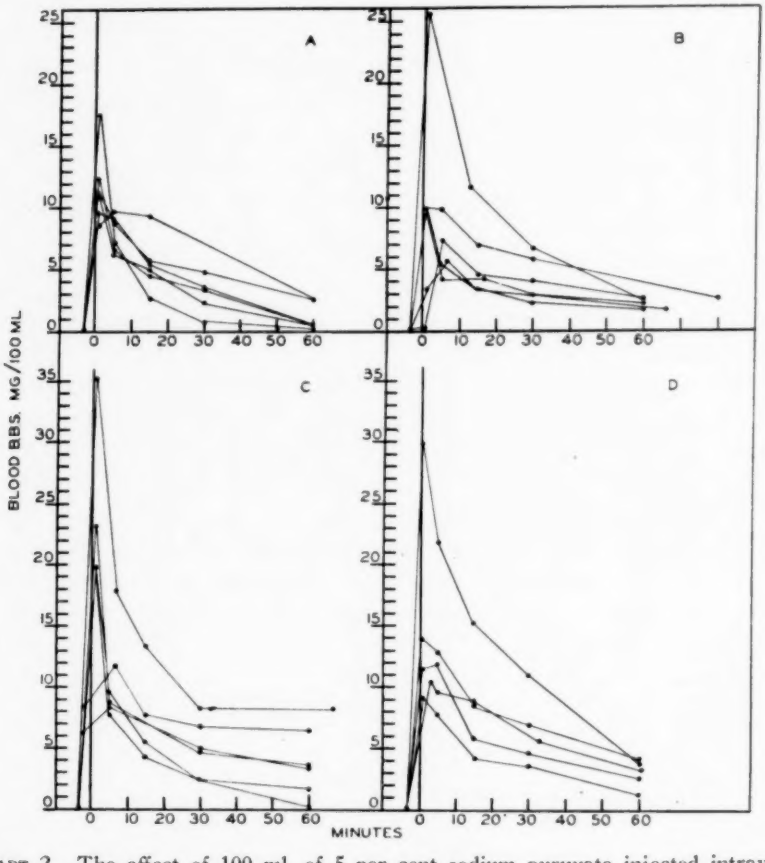

CHART 2. The effect of 100 ml. of 5 per cent sodium pyruvate injected intravenously on the bisulphite binding substances of the blood in (A) normal subjects; (B) patients without vitamin deficiency; (C) patients with "vitamin B deficiency," before treatment; and (D) patients with "vitamin B deficiency," after treatment.

the presence of appreciable amounts of pyruvate in the blood. The effect of pyruvate infusion on the blood sugar is regarded as inconsequential. There was no appreciable change in non-protein nitrogen. The carbon dioxide capacity usually increased 4 to 6 volumes per cent shortly after the injection, but returned to its previous level in an hour. This minor change was due to the administration of the sodium salt.

One of the uniform effects of sodium pyruvate was on the electrocardiograms, which showed lengthening of the Q–T interval, calculated as K, and minor but definite decrease in the amplitude of the T-waves. These changes appeared shortly after the injection and subsided in the course of an hour. Figure 1 shows the type of electrocardiographic changes produced. They are qualitatively the same as we have observed and as others [19] have reported following the intravenous and oral administration of sodium bicarbonate, and probably result in part from temporary alkalosis. In most cases the electrocardiographic changes were quantitatively greater after the

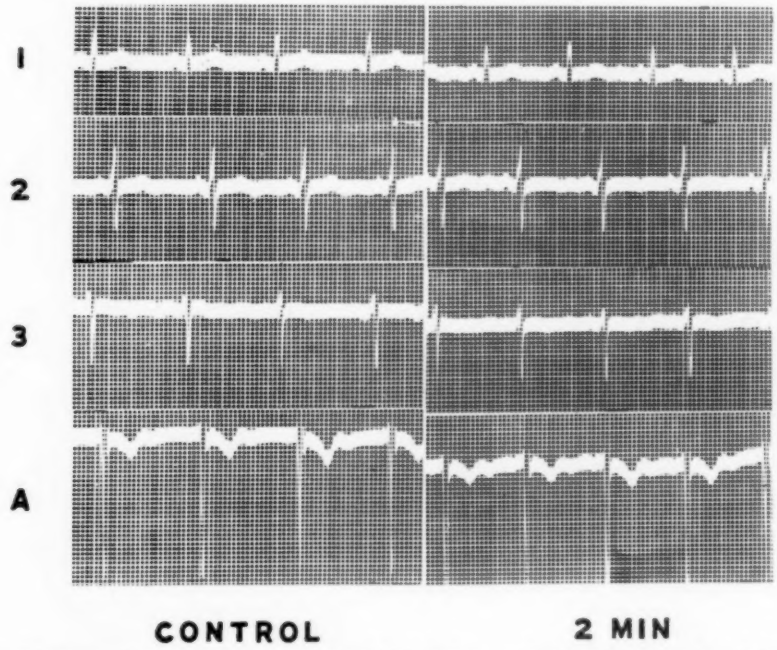

FIG. 1. Electrocardiogram of a normal subject before and two minutes after intravenous injection of 100 ml. of 5 per cent sodium pyruvate.

administration of sodium pyruvate than after the administration of comparable amounts of sodium bicarbonate.

2. *Patients Without Vitamin Deficiency.* Table 2 summarizes the results of intravenous injection of 100 ml. of 5 per cent sodium pyruvate in patients without vitamin deficiency. Chart 2B shows the blood B.B.S. curves. It will be seen that except for the greater initial rise in the patient with diabetes, who weighed only 100 pounds, and the slighter rises in those patients with edema or ascites, there were no distinctive differences from the normal controls. It may be that the physical factor of dilution of the pyruvate in a lesser or greater amount of body fluid caused the initial differences observed.

3. *Patients with "Vitamin B Deficiency."* Table 3A summarizes the

TABLE II

PATIENTS WITHOUT "VITAMIN B DEFICIENCY":

Intravenous Infusion 100 ml. 5 Per Cent Sodium Pyruvate

Patient No.	Diagnosis	Blood B.B.S. (mg./100 ml.)				Blood Sugar (mg./100 ml.)			Plasma CO_2 Capacity (vol. %)			Urine Pyruvic Acid	Electrocardiogram "K"	
		Initial Value	Change After Injection			Initial Value	Change After Injection		Initial Value	Change After Injection		No. Hrs. Positive	Change	Time of Change (min.)
			Immediately	5 min.	1 hour		5 min.	1 hour		5 min.	1 hour			
1	Rheumatic aortic and mitral disease; moderate congestive failure	7.20	+ 9.95	+ 5.40	+1.77	115.9	−0.6	−2.9	51.5	+5.4	—	5½	(Auric. fibrillation)	
2	Luetic heart disease; aortic regurgitation; severe congestive failure	4.19	+ 3.35	+ 5.64	+2.18	72.0	0	+3.3	56.0	+2.2	−0.3	8+	"	"
3	Rheumatic aortic disease; mild congestive failure	3.37	+ 0.19	+ 7.25	+2.49	95.3	−4.8	+0.7	61.1	+0.1	+2.3	9+	"	"
4	Cirrhosis of liver; ascites; edema	4.07	+ 9.40	+ 4.02	+1.72	109.0	+0.5	−2.9	64.3	+0.5	—	7+	+0.06	2
5	Arsphenamine hepatitis	4.50	+ 9.95	+ 9.87	+2.60 (80 min.)	100.5	+0.5	−3.1	—	—	—	6+	+0.03	2
6	Diabetes mellitus	4.37	+25.51	+11.75 (12 min.)	+2.55	146.6	+9.4 (12 min.)	−8.6	62.2	+5.6 (12 min.)	—	4	+0.04	2

TABLE III

PATIENTS WITH "VITAMIN B DEFICIENCY":

Intravenous Infusion 100 ml. 5 Per Cent Sodium Pyruvate

Patient No.	Diagnosis	Blood B.B.S. (mg./100 ml.)				Blood Sugar (mg./100 ml.)			Plasma CO_2 Capacity (vol. %)			Urine Pyruvic Acid	Electrocardiogram "K"	
		Initial Value	Change After Injection			Initial Value	Change After Injection		Initial Value	Change After Injection		No. Hrs. Positive	Change	Time of Change (min.)
			Immediately	5 min.	1 hour		5 min.	1 hour		5 min.	1 hour			
		A. *Before Treatment*												
7	Severe "wet" (cardiovascular) beriberi	9.61	+23.09	+9.69	+1.67	131.8	+5.2	+12.1	49.5	+7.5	+5.2	8½ + +(?24)	−0.02	30
8	Severe polyneuritis and psychosis; mild cardiovascular symptoms	3.97	+19.88	+ 8.86	+3.76	93.4	+3.7	−3.9	54.9	+8.3	+4.4	6	+0.03	6
9	Severe polyneuritis; psychosis	5.79	+35.16	+17.81	+8.15	93.4	+1.6	+9.7	55.4	−2.0	−9.6	——	+0.02	9
10	Mild polyneuritis	5.70	+19.85	+7.60	+0.28	89.9	+2.1	+1.4	64.0	−0.8	——	4½ +	+0.05	10
11	Pellagra	6.60	+8.43	+11.77	+6.27	109.8	+14.8	+4.5	63.7	+2.9 (imm.)	+0.4 (15 min.)	10 +	+0.06	2
12	Mild polyneuritis; psychosis	3.67	+6.10	+8.34	+3.43	110.5	−5.0	−1.5	57.3	−2.4	−2.8 (2 hrs.)	8	+0.04	2
	Treatment	B. *After Treatment*												
7	30 Days 910 mg. B_1—10 days Orange juice, Vegex and cod liver oil—20 days	3.43	+10.37 (3 min.)	+9.62	+3.42	93.3	−11.0	+0.4	65.4	−0.9	+4.0	4½ + +	+0.01	53
8	5 Days—350 mg. B_1	5.09	+11.44	+11.86	+2.61	87.2	+0.5	+9.9	65.0	+6.2	+1.5	4½ + +	+0.05 +0.02	1 8
9	2 Days—170 mg. B_1	13.80	+29.85	+21.80	+3.60	73.5	+6.4	−2.7	51.6	+3.6	+4.2	——	+0.05	2
10	5 Days—230 mg. B_1	3.81	+9.05	+7.74	+1.23	91.8	−6.8	−0.2	59.3	+4.8	——	4½ +	+0.02	10
11	6 Days—255 mg. B_1	4.16	+13.89	+12.80	+4.12	113.0	+10.5	−0.8	68.8	+2.9	−1.7	10	+0.03	1 and 8

effects of intravenous injection of 100 ml. of 5 per cent sodium pyruvate on patients with untreated "vitamin B deficiency." Table 3B shows the results in the same subjects after treatment with large parenteral doses (50 to 100 mg. a day) of crystalline vitamin B_1. Charts 2C and 2D show the B.B.S. curves. There were no significant differences in the pharmacological action of sodium pyruvate on the "vitamin B deficient" patients and on the normal controls, as indicated either by symptoms or by the cardiovascular measurements taken. There were, however, some differences in the B.B.S. curves of these patients and of the normal controls, and slighter differences among the group before and after treatment. Some of the deficient patients showed a tendency to continued elevation in the B.B.S. at the end of one hour. The results in patient 9 require explanation. This patient was psychotic and could not be prevailed on to take fluids. The great rise in B.B.S. after injection and the continued high level at the end of the hour may have been partly due to dehydration. After treatment with vitamin B_1 her tolerance to pyruvate was essentially the same except that the B.B.S. at the end of the hour was not so high. The patient at this time had been given fluids by stomach tube and was less dehydrated. The immediate high rise in some of the deficient patients before treatment may have been due to the rapid circulation characteristic of this disease.[8, 20]

B. Oral Administration of Sodium Pyruvate

Table 4 shows the effects of 100 ml. of 5 per cent sodium pyruvate and of 250 ml. of 10 per cent pyruvate by mouth. Except for the slower entrance into the blood stream by gastrointestinal absorption, there were no essential differences in the chemical findings from those in the intravenous experiments. In all cases with the large oral doses of 250 ml. of 10 per cent solution, however, there was a cathartic effect, characterized by moderate, watery diarrhea without severe abdominal cramps. In one subject (No. 8) this effect may have been great enough to interfere with absorption, but in the others the diarrhea did not become urgent until four hours had elapsed. In one subject (No. 7) dehydration from this cause was great enough to result in ketosis with acetone and diacetic acid in the urine after seven hours. The cathartic action continued for about 12 hours. The possibility that a large factor in the cathartic effect was simply the action of a hypertonic sodium solution could not be entirely ruled out. When the same amount of sodium pyruvate was given as a 2.5 per cent solution the cathartic effect was still present. In this case the large volume of fluid itself may, however, have contributed to this action. In the intravenous experiments no gastrointestinal symptoms were complained of, although the level of the pyruvate in the blood was usually much higher than that reached in the oral experiments.

TABLE IV

Oral Administration of Sodium Pyruvate

Subject No.	Diagnosis	Amount	Blood B.B.S. (mg./100 ml.)				Blood Sugar (mg./100 ml.)			Plasma CO_2 Capacity (vol. %)			Urine Pyruvic Acid	Electrocardiogram "K"	
			Initial Value	Change After Injection			Initial Value	Change After Injection		Initial Value	Change After Injection		No. Hrs. Positive	Change	Time of Change (min.)
				1 hour	2 hours	3 hours		1 hour	2 hours		1 hour	2 hours			
	A. *Normal Subjects*														
7	No disease	100 ml. 5%	5.80	+3.05	+0.87	—	84.8	+ 0.3	− 2.5	57.6	+4.1	—	6½	+0.01	30
8	No disease	100 ml. 5%	4.51	+1.87	+0.66	+0.22	90.5	− 4.3	0	57.5	+5.1	+3.2	7	+0.02	63
7	No disease	250 ml. 10%	5.83	+5.35	+7.04	+6.45	104.8	−11.8	−11.4	59.4	—	+5.4	12	+0.06	120
8	No disease	250 ml. 10%	4.05	+7.93	+5.01	+7.79	79.5	+ 1.9	+15.8	59.6	—	+4.7	11½+	+0.01	30
9	No disease	250 ml. 10%	3.43	+5.92	+7.30	+6.42	97.3	− 1.8	− 4.5	62.4	—	−0.6	10	+0.04	65
Pt. No.	B. *"Vitamin B Deficient" Patients After Treatment*														
7	Beriberi	100 ml. 5%	5.13	+1.67 (75 min.)	+1.35	—	93.0	—	− 1.7	58.6	—	+2.6	7++	+0.01	60
12	Mild polyneuritis; psychosis	100 ml. 5%	3.40	+2.27	+1.42	+0.06	104.2	+ 0.6	− 0.6	55.2	+5.1	—	9½	+0.02	33
7	Beriberi	250 ml. 10%	3.00	+2.75	+6.05	+7.70	104.2	−18.0	−18.9	67.4	+4.5	—	7++	+0.02	125
12	Mild polyneuritis; psychosis	250 ml. 10%	4.34	+6.07	+7.34	+10.16	133.3	−23.5	−24.3	50.4	—	+10.0	10++	+0.01	120 65

Discussion

While pyruvic acid is an intermediary product of carbohydrate metabolism and represents a stage of oxidation at which theoretically catabolism results in formation of carbon dioxide and water, or anabolism produces lactic acid and glucose, it is usually not formed in the human body in amounts sufficient to raise the B.B.S. of the blood or to allow detection in the urine by sensitive qualitative test. Increased amounts of pyruvic acid have been reported, however, not only in normal subjects after strenuous exercise,[21] but also in patients with vitamin B_1 deficiency [4, 10] and in patients with diabetes mellitus.[10, 22] The problem of whether pyruvic acid can be utilized by the animal organism as an antiketogenic substitute for glucose or higher carbohydrates has stimulated investigations, with divergent results and conclusions.[23, 24, 25, 26, 27, 28, 29]

So far as may be judged from the acute experiments here reported, sodium pyruvate in the doses employed is essentially non-toxic for man. It produces no untoward symptoms, and with the exception of prolonging the period of electrical systole, probably due to transient alkalosis, it exerts no significant effects on the cardiovascular system or the blood chemistry. The cathartic action of the substance after oral administration is mild and of short duration. There is also experimental evidence that sodium pyruvate has such an action on the surviving gut.[2, 30, 31, 32] It may be that chronic excesses of pyruvate may produce these same effects to a greater degree, or may even result in other "toxic" reactions. The present study offers no direct evidence on this point.

With the method used, sharp differences were not found in the pyruvate "tolerance" of normal and of "B" avitaminotic human beings, such as Sherman and his coworkers reported in chicks. It may be that in normal human beings the ability to metabolize pyruvic acid is relatively slight in comparison with that in normal birds, so that any difficulty superimposed by vitamin deficiency is less apparent. The prolonged presence of pyruvic acid in the urine following intravenous infusion indicates that in normal man, at least, pyruvate is not rapidly metabolized. The amount and rate of the pyruvate infusions may therefore have been too great to allow clear-cut distinction of small differences. It is possible that with a different dosage of the pyruvate infusion sharper differences could be brought out. In the light of experience so far, the period during which the differences in metabolism become apparent seems to follow the first half hour after pyruvate injection. Thus not only the degree but also the duration of elevation of the blood pyruvate may be of significance in the comparison of the response of normal subjects with that of patients with B_1 deficiency.

The bisulphite binding capacity of the blood represents only an indirect measurement of pyruvic acid. It is possible that certain ketone bodies arising from the metabolism of pyruvate may bind bisulphite and contribute to the high values. Preliminary studies of the blood pyruvic acid measured directly support this possibility.[33]

Summary and Conclusions

1. The pharmacological action of sodium pyruvate administered intravenously and orally in normal and diseased human beings has been studied.

2. Prolongation of the electrical systole and, following oral administration, mild catharsis, were the only constant effects of sodium pyruvate observed. The cardiac effect may be attributed to transient alkalosis, and the cathartic effect to hypertonicity of the solution administered.

3. Following pyruvate infusion in normal subjects the blood pyruvate, as measured by the bisulphite binding substances in the blood, rose sharply and then gradually fell toward its original level in the course of an hour. The non-protein nitrogen and the glucose content of the blood were not significantly altered.

4. As measured by sensitive qualitative test, pyruvic acid was excreted in the urine of normal subjects as soon as 15 minutes and as long as six hours after intravenous injection.

5. Some of the patients with " B " avitaminoses showed a tendency to a more prolonged elevation of the blood B.B.S. after intravenous injection of pyruvate. Clear-cut differences from the normal B.B.S. curves, however, were not apparent in every case of " vitamin B deficiency."

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ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS—A SYSTEMIC DISEASE*

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The cutaneous lesions included in the term lupus erythematosus fall into the so-called erythema group of skin disorders. Since they are entirely distinct from lupus vulgaris, and since a tuberculous etiology has not been proved for them, it is unfortunate that the term "lupus" is part of their nomenclature. Many elaborate classifications have been proposed for this group of lesions, but most of them are needlessly complex, and are based upon more or less artificial morphologic variations. For our purposes it will be sufficient to divide them roughly into two large groups: (1) the chronic fixed or discoid type, and (2) an acute or subacute, often recurrent, type marked at times by widely disseminated and polymorphic lesions of the skin and mucous membranes, with constitutional symptoms, frequent widespread visceral involvement, and a variable clinical picture. This second type, the acute disseminated form of lupus erythematosus, is a disorder in which (as is so often the case in so-called skin diseases) the cutaneous lesions are merely part of a widespread general morbid process; it is so frequently associated with major visceral lesions and constitutional symptoms that it is of unusual importance to the internist and general practitioner. We wish to emphasize particularly those aspects of the disease which pertain to the field of internal medicine.

In our present state of knowledge the diagnosis must rest largely upon recognition of the skin lesions. A brief description of them and a comparison with the lesions of the chronic discoid form of lupus erythematosus is therefore necessary.

The chronic discoid form is much more common than the acute disseminated variety, and only rarely does it exhibit rapid extension or associated systemic manifestations. The lesions occur chiefly in parts exposed to light (face, nose, forehead, ears, dorsum of the hands, neck, etc.) and appear as scaling patches of varying size and color—they usually range from light pink to dark reddish brown. There is often hyperpigmentation; in long standing cases, marked atrophy and depigmentation of the skin occur. The lesions tend to extend slowly; the edges are sharply defined, and often infiltrated. The most characteristic feature of chronic lupus erythematosus, aside from its distribution on the malar prominences and the bridge of the nose, in a majority of cases, is the follicular dilatation and plugging seen in the active portion of the lesion, usually at the periphery.

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The initial change takes place in the hair follicles, and small erythematous comedone-like papules are seen. The follicular plugs are hard and horny, however, and cannot be expressed from the follicle as can ordinary comedones. Marked progress often requires months or years. Occasionally, especially after trauma, exposure to cold or actinic irradiation, tuberculin injections or gold therapy, the typical picture of the acute disseminated form may be engrafted upon the chronic discoid type.

In the acute disseminated variety the lesions are often polymorphic and are usually active. The entire gamut of lesions seen in the erythemas may be encountered; a relationship to erythema multiforme has been suggested.[1] The exposed areas of the body are the sites of predilection, but no cutaneous or mucous surface is immune. The typical initial lesion appears (usually on the face or nose) as a small, often impalpable, erythematous patch, which usually spreads rapidly. The so-called bat-wing or butterfly configuration across the cheeks and nose is characteristic. The affected area may rapidly extend to include the entire face, ears, neck and upper trunk. A wide variety of lesions may occur, simultaneously or in succession—livid edematous urticaria-like or erysipeloid areas, purpura, showers of petechiae, or reddish-brown to purple macules, eczematoid patches, bullae, telangiectases, crusted areas, or ulcers. The vermilion border of the lips may show edema, crusting, fissuring, or ulceration. The mucosal lesions usually begin as sharply defined patches of erythema, often followed by ulceration and purulent exudate; hemorrhagic lesions are common on the mucous surfaces. In one of our cases the first lesions observed were in the pharynx. While no single skin lesion is characteristic of all cases of acute lupus erythematosus, the most common and persistent change is a deeply erythematous swollen patch or plaque of varying size. When this occurs on the cheeks, the appearance may suggest erysipelas strongly, but the erythema is usually more livid, and progression of the margin less rapid. When remission occurs, marked atrophy and scarring or pigmentation may follow the subsidence of the cutaneous lesions.

A comparison of the chief clinical features of the acute disseminated and the chronic forms of lupus erythematosus is shown in table 1.

The clinical course of acute disseminated lupus erythematosus is extremely variable. Females are much more commonly affected than males and are especially susceptible between puberty and the menopause. The onset may be abrupt, and the course short and stormy, with a fatal termination in six or eight weeks. At the other extreme are cases marked by mild systemic reactions and prolonged remissions during which all cutaneous or visceral manifestations may disappear. Between these two extremes a wide variety of nosologic types is seen. The mortality of the disease is high: probably more than 90 per cent of cases end fatally within five years. A striking characteristic is the tendency for acute cutaneous and systemic manifestations to appear or recur after exposure to sun or ultraviolet light, roent-

gen-rays, insect bites, cold, or the intracutaneous injection of irritating substances such as tuberculin. The clinical course is at times dramatically unexpected—a patient who seems almost moribund may occasionally recover, or a tiny patch of facial erythema may initiate a fulminating and rapidly fatal illness. Renal failure, broncho-pneumonia, "toxemia," or terminal bacteremia are the commonest causes of death. The onset of the acute frank manifestations is sometimes preceded by a prolonged period of vague ill-health, often marked by grippe-like attacks, recurrent bouts of fever, malaise, purpuric phenomena, or arthralgia. A number of recurrent seasonal exacerbations of the skin lesions may precede the onset of systemic disturbances. One of our patients suffered an annual outbreak of facial lesions every summer for 24 years except one year when he was working at night. The final exacerbation ushered in a fatal phase of systemic involvement.

TABLE I

Comparison Between Chronic Discoid and Acute Disseminated Forms of Lupus Erythematosus

Chronic discoid	*Acute disseminated*
Slow course of skin lesion (weeks or months).	More rapid course (days or weeks).
Lesions uniform	Lesions polymorphic
Scaling, moderately erythematous, pigmentation, atrophy, scarring.	Erythema, urticaria, diffuse swelling, purpura, petechiae, bullae.
Rarely systemic reaction or leukopenia.	Almost always severe systemic reaction and leukopenia.
Localization—tendency to light-exposed areas.	Localization—light-exposed or traumatized areas.
Mucous membrane lesions uncommon (except lips).	Mucous membrane lesions common (lips, mouth, pharynx, etc.).
Skin involvement—rarely extensive.	Involvement sometimes limited but usually extensive in acute phase.
Scarring almost always.	Often no scarring.
Treatment—moderately effective (bismuth, gold, ointments, local destructive measures, cautious removal of foci, ultraviolet light—*never;* roentgen-ray—sometimes).	Treatment—highly ineffective (bismuth—maybe, gold—never; removal of foci, *never* during acute phase; ultraviolet light—*never;* roentgen-ray—*never*

ment. Evidence of visceral involvement may precede the appearance of the skin lesions, or persist during periods of complete cutaneous remission. Fever, usually sustained and often high, is practically constant during the acute phases of the disease. Septic foci may develop in the viscera, lymph nodes or subcutaneous tissues, and their appearance often presages a terminal phase of the disease.

The cause of acute disseminated lupus erythematosus remains unknown. It has long been regarded by many writers as a manifestation of tuberculous infection or as an allergic response to tuberculo-toxin—this view appears to be based largely on the occasional finding of active tuberculous lesions in patients with the disease, upon the alleged recovery of tubercle bacilli from the blood stream in some cases, and upon the marked response which usually occurs after tuberculin inoculation. After reviewing the evidence, however, we agree with Keil [2] that proof of a tuberculous etiology is lacking,

and that the coincidence of active tuberculosis is not necessarily significant. An infectious or "toxic" etiology is strongly suggested by the clinical features of the disease. Various organisms have been recovered from the blood stream and focal lesions, including various streptococci, pneumococci, staphylococci, *B. pyocyaneus,* and others. There is no proof, however, that these have been other than coincidental or terminal invaders. Blood cultures are persistently sterile in the great majority of cases. It has been suggested that toxic products may be formed in the skin of certain persons, perhaps following exposure to actinic irradiation or various types of trauma, and that these noxae may, directly or indirectly, attack that part of the vascular system which bears the brunt of the disease. Skin sensitization to abnormal products of the reticulo-endothelial system, or sensitization to various metabolites (urea, hematoporphyrin, tyrosine, lactic acid, lymphocytic ferments, etc.) have been suggested as possible causes. Ludy and Corson [3] have recently reported the presence of hematoporphyrinuria and of lead in the skin in a series of cases observed in Philadelphia—they believe the disease to be increasing in frequency in this locality.

The histo-pathology of the disease appears to be compatible with the action of a "toxic," as distinguished from an infectious, agent. Keil [4] has recently advanced a concept of the disease which regards it as the expression of a widespread vascular disease process, of unknown etiology, involving chiefly the capillaries and to a lesser extent the arterioles and venules, with some extension into the perivascular spaces; such a concept would appear to agree with the clinical and pathological phenomena of the disease. This vascular predilection would explain the wide variety and the variability of visceral involvement, and the protean clinical nature of the disease. Lewis [5] has pointed out that the cutaneous areas most often affected are those in which the capillaries are of the "atonic" type (i.e., they fail to respond normally to the injection of vasoconstrictor substances). The characteristic vascular lesions have been described by Baehr, Klemperer, and Schifrin [6] as consisting of (1) capillary dilatation with extravasation of blood and serum; (2) proliferative endothelial vascular lesions with thrombus formation; and (3) degenerative or necrotizing lesions in the walls of capillaries, arterioles and venules, often with hemorrhage into adjacent tissues. All three processes may be found in the same case, and in any part of the vascular tree. Hyaline capillary thrombi are characteristic and widespread.

More or less obscure relationships exist between acute disseminated lupus erythematosus and certain other syndromes:

(1) Thrombocytopenic purpura may precede, accompany, or follow the syndrome of acute erythematous lupus. In these cases the spleen is usually enlarged and the hematologic findings are typical. Keil [7] believes that the thrombocytopenia in such cases is due largely to the inclusion of platelets in the numerous hyaline thrombi which occur characteristically in the capillaries. Two cases are cited by him in which classical thrombocytopenic

purpura disappeared after splenectomy, with the development of fatal disseminated lupus erythematosus some months later. Thrombocytopenia, splenomegaly, and hemorrhagic phenomena are quite common in the course of the disease as more or less periodic phenomena.

(2) Raynaud's disease occasionally precedes or accompanies acute disseminated lupus erythematosus. Füllenbaum and Sosin [8] have recently reported such a case, in which necrosis of the spleen was found at necropsy. One of our patients, a 38 year old mulatto woman, presented the picture of Raynaud's disease for about 3 years, associated with occasional showers of tender petechiae on the hands and feet; she then developed a typical acute exacerbation of disseminated lupus erythematosus with abdominal pain, fever, petechiae, menorrhagia, splenomegaly, leukopenia, anemia, and thrombocytopenia. The lupus lesions were confined to the face, gums, ears, and scalp. The acute phase subsided, leaving her in a remission but with persistent anemia, leukopenia and thrombocytopenia, and showing occasional showers of petechiae. The skin lesions became pigmented and have responded to cautious local treatment. It is of some corollary interest that Völk [9] has reported the coincidence of periarteritis nodosa with acute disseminated lupus erythematosus.

(3) In 1895 Osler [10] reported under the name erythema exudativum multiforme a group of cases with polymorphic erythematous skin lesions associated with a variety of visceral lesions—acute nephritis in five cases, gastrointestinal or urinary bleeding in three and splenomegaly, endocarditis and pericarditis in others. It seems probable that some of those cases were identical with, or variants of, acute disseminated lupus erythematosus.

(4) The so-called Libman-Sacks syndrome [11] * is at times accompanied by skin lesions identical with those of acute disseminated lupus erythematosus. This syndrome appears to present a somewhat indeterminate picture, resembling in certain aspects both rheumatic fever and subacute bacterial endocarditis, but differing from both in important respects. Its chief clinical characteristics include arthralgia, fever, white-centered petechiae, purpura, endocarditis and pericarditis, pleuropulmonary complications, anemia, leukopenia, splenomegaly, hepatomegaly, embolic glomerulonephritis and other embolic phenomena, and ulcerative mucosal lesions. Blood cultures remain sterile. The course may be prolonged but the mortality is high, death often resulting from cerebral disasters or intercurrent infection. The characteristic pathologic finding appears to be a form of verrucous valvular and mural endocarditis which will be described later. It seems beyond doubt that those cases described by Libman and Sacks with erythematous facial lesions were examples of acute disseminated lupus erythematosus with visceral involvement. Whether their other cases represent instances of the same disease without erythematous skin lesions must remain uncertain for the present.

* Its existence as a nosologic entity has been questioned.[12]

Renal involvement is common, and renal failure is an important cause of death. The urinary findings are not consistently characteristic of any particular type of renal lesion, but merely indicate irritation or injury of the kidneys. The clinical picture may suggest any one of several kinds of kidney disease—glomerulo-nephritis, pyelo-nephritis, "diffuse" or "interstitial" nephritis, pyonephrosis, or tubular nephrosis. Baehr and his associates [6] reported that hypertension was uncommon in their cases; it was present, however, in four (one-third) of our patients. A variety of lesions has been described, including abscesses, tubular degeneration and necrosis, embolic glomerulitis, infarction, cloudy swelling, simple nephrosis, interstitial inflammatory change with cellular infiltration, and edema, "parenchymatous" and "hemorrhagic" nephritis, pyonephrosis, etc. Baehr, Klemperer and Schifrin [6] have described what they believe to be the characteristic renal lesion of the disease, and one which they report having seen in no other condition with the possible exception of the kidney of eclampsia. This consists of a peculiar hyaline thickening of the walls of the glomerular capillaries, giving what they call the "wire-loop" appearance —these loops contain no amyloid or lipoid material. Along with these changes they describe proliferative and thrombotic processes involving part or all of the glomerular vasculature; the picture may resemble that of the embolic glomerulo-nephritis seen in subacute bacterial endocarditis. Of our five cases which came to necropsy all showed significant glomerular lesions which will be discussed below. The clinical picture of nephritis may precede the onset of the cutaneous eruption, or persist when the skin lesions are in remission.

Equally important are the cardiac lesions which are found chiefly in the endocardium and pericardium. Dyspnea, tachycardia, and palpitation are common symptoms, but congestive failure occurs only occasionally, and even then is usually a late or terminal phenomenon. Electrocardiographic changes do not seem to be pathognomonic. Precordial murmurs are very common but in the presence of fever, anemia and tachycardia cannot be regarded as necessarily indicating endocarditis. The entire clinical picture may closely simulate bacterial endocarditis, and at times can be distinguished from it clinically only by the persistent sterility of blood cultures. The endocardial lesions may closely resemble those of acute rheumatic fever, but are usually bacteria-free on culture or section. The mitral and tricuspid valves are most frequently affected. In some cases evidence of healed valvular endocarditis has been found. Atypical verrucous lesions of the type described by Libman and Sacks [11] have been frequently reported. These are coarse, rather large, flat or wrinkled vegetations, frequently extending along the chordae tendineae and covering part of the mural endocardium. They are bacteria-free and on section are composed of hyaline-like thrombotic material, often with a superficial layer of freshly deposited platelets; they may be partially covered by endothelium. The subendocardial myo-

cardium may show degenerative changes, but Aschoff bodies and Bracht-Wachter lesions are said to be notably absent from the myocardium. Fibrinous pericarditis, with serous or serofibrinous effusion, is often found; pericardial frictions or the signs of effusion may give indication of such

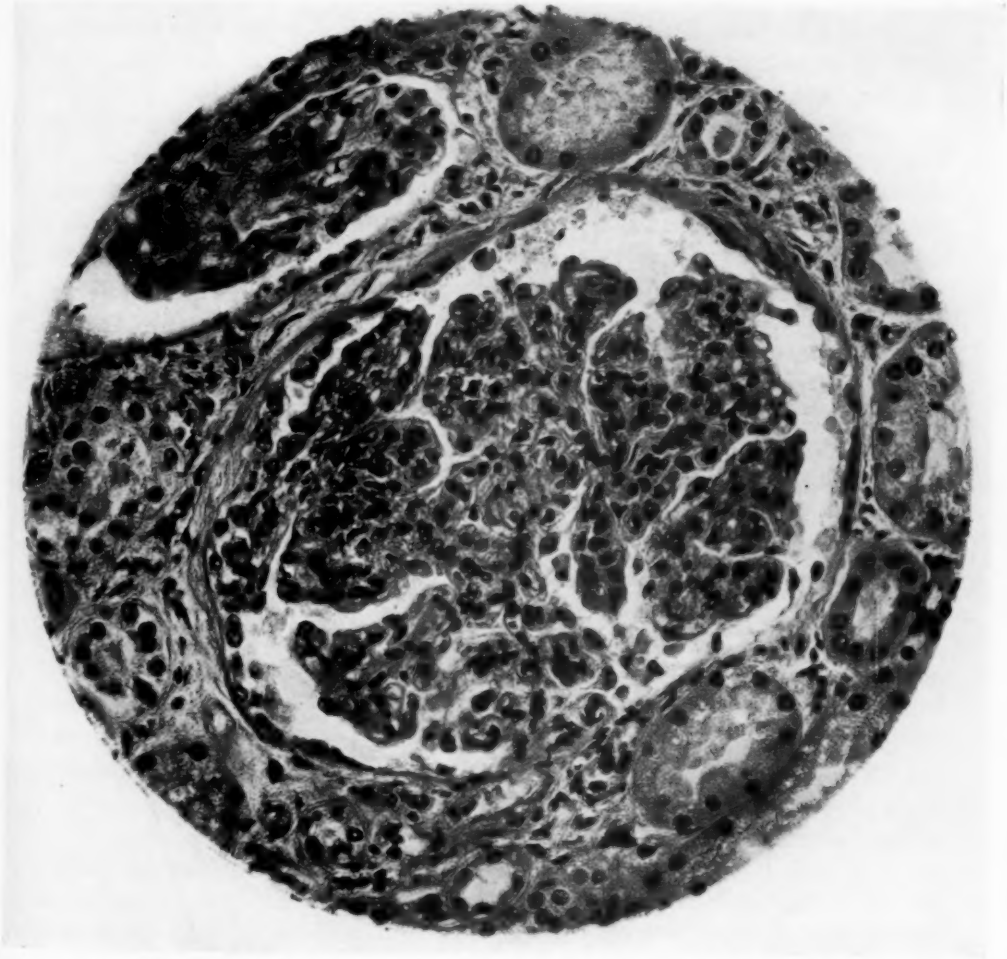

FIG. 1. Glomerular lesion (patient W. Z.) of acute disseminated lupus erythematosus. The glomerulus is large and richly cellular. In one area it has become fused or adherent to the capsular epithelium, which in that region shows moderate proliferation. Only two patent capillaries are seen and from them a few red cells have escaped into the capsular space. The remainder of the tuft is completely avascular.

processes during life. Endocardial lesions were found in only one of our five cases coming to necropsy, and in this instance the vegetations did not conform to the description of the Libman-Sacks variety. Another of our patients developed a large serous pericardial effusion but showed no sig-

nificant cardiac lesions at necropsy. Fibrinous pericarditis was found in one case.

Intra-ocular lesions are common. They include papilledema, sometimes with extension of the edema into and beneath the retina; retinal detachment and atrophy, guttate retinitis; perivascular exudates and hemorrhages, and choroidal degeneration. These lesions are not necessarily associated with renal disease, as they often occur in patients who present no evidence of kidney damage. They are probably a part of the widespread vascular disease.

Pulmonary complications are among the chief immediate causes of death. Bronchopneumonia, lobar pneumonia, abscess, gangrene, infarction and atelectasis are the most important. Severe tracheo-laryngitis is occasionally seen, and pleural effusion (usually serous, occasionally serofibrinous or purulent) is very common. Active pulmonary or tracheobronchial lymph node tuberculosis does not seem to occur with significant frequency.

Lymphadenopathy is likewise common, and may precede the appearance of the eruption. Both the superficial and deep lymphatic chains may be affected by suppurative or necrotizing changes. Active tuberculous lymphadenitis has been found in a number of cases.

Arthralgia may precede or accompany the eruption and systemic phases of the disease, and is sometimes mistaken for a symptom of rheumatic fever or infectious arthritis. Joint deformities have been reported. Serous, bloody, or purulent synovial effusions are common, and periarticular swelling occasionally occurs. The large joints appear to be more commonly affected.

Effusion may occur in any of the serous cavities. Reference has already been made to pleural and pericardial effusion; peritoneal effusion is less common, but may produce acute or subacute abdominal symptoms. This is also true of the mucosal lesions occurring in the gastrointestinal tract, and of embolic or thrombotic phenomena in the mesenteric circulation. Such processes may simulate acute abdominal emergencies so closely as to lead to unnecessary surgical exploration.

The liver is often enlarged as a result of cloudy swelling, acute congestion, pylephlebitis or abscesses. Jaundice is an occasional complication. The spleen frequently enlarges likewise, and may show parenchymatous degeneration, acute splenitis, acute congestion, necrosis with arteriolar obliteration, abscess, infarction, or perisplenitis. The typical clinical picture of acute splenic infarction may be recognizable, including the appearance of a perisplenic friction rub.

The principal feature of the blood picture is the leukopenia which is seen at some time in the course of the great majority of cases. In our experience this has been due to a roughly uniform reduction in the number of all the leukocyte forms, with perhaps some tendency toward a relative neutrophilic increase. The lymphocytosis mentioned by some writers [3] was

not evident in our cases. The leukopenia may persist during remissions. When leukocytosis occurs, it is seldom marked and usually accompanies some septic complication or the terminal phase of the disease. One of our patients showed occasional eosinophilia up to 8 per cent. Thrombocytopenia is well recognized, especially as part of the purpuric syndrome previously mentioned. During remissions the platelets may rise to normal levels. In the acute purpuric phases coagulation time may be prolonged and clot retraction may be abnormal. The sedimentation rate of the erythrocytes is frequently increased, and this increase may persist during clinical remissions. Hemorrhagic changes and a leukoblastic reaction in the bone marrow have been reported.[13]

The ulcerative lesions which occur in the mucosa of the gastrointestinal tract (including the mouth and pharynx), vagina and bladder may give rise to severe hemorrhage. Hematemesis occurred in two of our cases, and hemorrhagic cystitis was also present in one.

The significant data relating to 12 cases of acute disseminated lupus erythematosus which we have observed in the past six years are summarized in table 2. Eleven of these patients were seen at the Hospital of the University of Pennsylvania, and one was seen at the Children's Hospital of Philadelphia. It will be seen that nine patients were females, the majority being in the second and fourth decades. Nine patients have died, two are in remissions, and one shows a mild recurrence of the skin lesions without any evidence of systemic involvement at present. Pneumonia, renal failure, and "toxemia" were the chief causes of death. The uniform sterility of blood cultures, in the 10 cases in which this procedure was carried out, is striking. In the five patients who came to necropsy no evidence of active tuberculosis was found. Clinical or postmortem evidence of renal irritation or damage was present in 10 cases—hypertension occurred in four of these. Vascular lesions of varying degree in the glomeruli, similar to those described by Baehr and his associates, were found in all of the five patients coming to necropsy (hypertension had been present in none of them). The "wire-loop" appearance of the capillaries, focal necroses, and varying degrees of cellular proliferation, avascularity and ischemia were the chief characteristics. The inflammatory lesions of the glomeruli varied in severity from partial involvement of occasional tufts to well marked diffuse glomerulo-nephritis. The most frequent finding was rich cellularity and fusion of the component capillaries in isolated glomerular lobules; in some instances this was associated with foci of necrosis. No gross characteristic changes were seen in the kidneys. The pathological diagnosis was focal glomerulo-nephritis in three cases, and atypical diffuse glomerulo-nephritis in two. Cloudy swelling, abscess, and simple nephrosis were other changes found.*

The high incidence of leukopenia in our series confirms the consensus in

* The glomerular lesions were found only on reëxamination of the necropsy material, and were not reported in our original presentation.

TABLE II

Summary of Twelve Cases of Acute Disseminated Lupus Erythematosus

Case	Age	Sex	Color	Result	Duration	Remissions	Cause of Death	Systemic Manifestations	Hemogram					Comment
									W.B.C. (Thousands)	Hb. (per cent)	R.B.C. (Millions)	Platelets (Thousands)	Sed.Rate R.B.C.	
A. C.	20	F.	White (Italian)	Death	3 mos.	None	"Toxemia," Bronchopneumonia	Bronchopneumonia. Serous pleural and pericardial effusions. Adenopathy. Arthralgia. Focal glomerulo-nephritis.*	3.9 to 6.6	50 to 78	3.2 to 4.1	140 to 425	+	Renal function normal. Large serous pericardial effusion. Hemolytic *Staphylococcus aureus* recovered from bone marrow during life.
G. D.	30	F.	White	Death	4 years	4 or 5	Bronchopneumonia	Arthralgia. Bronchopneumonia and pleurisy. Acute verrucous endocarditis (mitral); cardiac hypertrophy. Septic splenitis with splenomegaly. Ulcers on palate and nasal septum. Focal glomerulo-nephritis.*	2.9 to 13+	48 to 87	3.0 to 3.9	204 to 380	+	Arthralgia with each exacerbation. Marked albuminuria. Exacerbations usually occurred in summer.
W. Z.	25	M.	White	Death	3 mos.	None	Bronchopneumonia	Hemorrhagic splenitis. Fatty degeneration of the liver. Bronchopneumonia. Atypical diffuse glomerulo-nephritis.*	2.3 to 10+	72 to 92	4.1 to 4.4	.....	....	Marked albuminuria. Terminal slight azotemia. Loss of 27 pounds. Glomerular lesions very marked.
G. E.	39	M.	White	Death	24 years. (Acute terminal phase 2½ months	24 (Winter remissions)	Renal failure Bronchopneumonia	Acute splenic tumor. Fatty infiltration of liver. Bronchopneumonia. Fibrinous pericarditis and myocardial degeneration. Atypical diffuse glomerulo-nephritis.*	7.8 to 21+	68 to 85	4.4	320	+	Annual summer exacerbation of skin lesions for 24 years (missed one summer when he did night work). Albuminuria and terminal azotemia.
E. C.	16	F.	White	Death	8 weeks	None	"Toxemia" Bronchopneumonia	Bronchopneumonia, atelectasis, pleural effusion. Multiple liver abscesses. Solitary renal abscess; focal glomerulo-nephritis. Hemorrhagic cystitis. Stomatitis. Epicarditis.*	3.0 to 7.5	52 to 84	2.6 to 4.3	.....	....	Fulminating course with rapid spread of skin lesions. Hematemesis. Stomatitis. Renal function moderately reduced. Hypochloremia.
E. E.	19	F.	White	Death	Uncertain, at least 1 year	Probably 2 (Partial)	Unknown	Arthralgia. Adenopathy. Papilledema. Pericarditis. Pleurisy with effusion. Enlargement of liver and spleen. Albuminuria. Hypertension.	4.3 to 10.5	54 to 100	3.2 to 4.8	.....	....	Acute exacerbation after cauterization of cervix. Renal function moderately impaired. Hypoproteinemia. Died after leaving hospital.

TABLE II—*Continued*

Case	Age	Sex	Color	Result	Duration	Remissions	Cause of Death	Systemic Manifestations	Hemogram					Comment
									W.B.C. (Thousands)	Hb. (per cent)	R.B.C. (Millions)	Platelets (Thousands)	Sed. Rate R.B.C.	
M. D.	64	F.	White	Death	6 mos.	None	Renal failure	Clinical picture of severe nephritis, with vomiting, hypertension, azotemia, albuminuria, cylindruria, reduction of urinary specific gravity, hypoproteinemia.	4.0 to 5.2	64 to 67	2.6 to 3.6	.....	....	Renal failure dominated the clinical picture. Died after leaving hospital.
V. A.	38	F.	Mulatto	In remission	Uncertain, probably 2 or 3 years	Two	.....	Abdominal pain, purpura, petechiae, cardiac murmurs, splenomegaly, menorrhagia, pneumonia(?) and pleural effusion, albuminuria and cylindruria. Moderate reduction of renal function.	4.5 to 13.9	48 to 82	2.6 to 4.2	80 to 308	+	Raynaud's symptoms for 2 years + prior to onset of acute phase. Two exacerbations with thrombocytopenic purpura and severe abdominal pain. Now in remission with anemia, leukopenia and increased sedimentation rate of red cells.
H. K.	17	F.	White	Death	5 mos.	None	"Toxemia"	Papilledema and retinitis. Arthralgia, purpura, hypertension, albuminuria, hematuria and cylindruria. Splenic infarction. Pleural and peritoneal effusions.	4.3 to 15.0+	28 to 67	1.7 to 4.0	145 to 281	....	Exacerbation after exposure to sunlight. Arthralgia, edema and purpura on legs were earliest symptoms.
M. B.	34	M.	White	Death	1 year	One	Unknown	Arthralgia. Adenopathy. Bronchopneumonia. Systolic mitral murmur. Hypertension. Albuminuria. Ulcerative sore throat.	5.0 to 14.0+	60 to 100	3.7 to 5.1	128 to 323	....	Exacerbation after ultraviolet therapy. Lesions on ears preceded acute phase by about 9 months.
A. B.	25	F.	White	Still alive. (Recurrence)	3 years	One, lasting about 2 years	.....	Cervical lymphadenopathy. No cardiac, renal, or pulmonary manifestations.	3.4 to 6.0	82 to 88	4.3	115 to 202	Normal	Increasing sensitivity to sunlight, with annual summer erythema for 4 years before acute phase.
G. F.‡	11	F	White	Remission	9 mos.	Two	.....	Acute otitis. Faint systolic apical murmur.	4.0 to 5.9	76 to 80	4.1 to 4.2	256	+	In complete cutaneous remission for 4 years when last seen, but still has leukopenia, anemia and increased sedimentation rate. Some delay of development of secondary sex characters.

* Confirmed by necropsy.
† Terminal.
‡ Blood culture not done—blood cultures sterile in all other cases.

the literature. Eleven of our patients exhibited leukopenia at some time during their disease; this persisted during most of the period of observation in the majority of cases, although leukocytosis occurred sporadically in seven instances.

The importance of light-sensitivity in this disease is borne out by the fact that six of our patients developed their initial eruption, or a cutaneous exacerbation, immediately after exposure to sun- or ultra-violet light. Three patients gave histories indicating abnormal sensitivity to sunlight for months or years prior to the onset of the acute phase of their disease.

It may properly be asked whether the visceral lesions of the acute disseminated lupus erythematosus syndrome may exist in the complete absence of cutaneous lesions—whether there may be such an entity as *lupus sine lupo*. The description of some of the cases without skin lesions reported by Baehr [14] and by Libman and Sacks [11] strongly suggests that they may have been examples of such a syndrome, but until the disease can be reproduced experimentally or until its cause is known, it seems unlikely that the existence of such a non-eruptive form can be translated from an hypothesis into a fact. Meantime, however, it would seem proper to consider the possibility of such an entity in a patient with fever, leukopenia, petechiae or purpura, embolic phenomena, arthralgia, evidence of endocarditis, pericarditis, renal injury, pleural effusion, and persistently sterile blood cultures.

The high mortality of acute disseminated lupus erythematosus is ample evidence of the inefficacy of treatment. A large number of therapeutic agents have been employed, none of which is consistently effective. It is perhaps more important to know what to avoid than what to use in treatment. The dangers of exposure to sunlight (even when filtered through glass) and ultra-violet light have previously been mentioned; patients should carefully avoid such exposure even when in remission, or if suffering from the chronic form of lupus erythematosus. In the treatment of the acute phase the patient should be kept in a darkened room. Too frequent exposure to roentgen-rays should be avoided. The removal of focal infection is often followed by severe exacerbations, and should if possible be avoided during acute phases. In the chronic form of the disease, or during remissions, foci of infection should be attacked with great caution, not more than one focus being removed at a time. Likewise the injection of tuberculin into or beneath the skin may be followed by a serious exacerbation, and should be avoided. The use of gold salts during acute phases of the disease, or in remissions, is highly dangerous.

The use of protective creams or ointments, especially those containing quinine, is often helpful. Other local measures for the softening or removal of crusts, wet dressings for septic foci in the skin, the treatment of decubitus ulcers, oral hygiene, etc. are of course frequently indicated. General therapeutic agents which have been tried include blood transfusions, whole blood injections intramuscularly, pentose nucleotide, lyophilized convalescent scarlet fever serum, polyvalent anti-streptococcic serum, sulph-

anilamide, liver extract, vitamin B concentrate, quinine, intramuscular bismuth injections and plasmochin by mouth or intravenously. Most of these have been employed in our cases with no evidence of any specific effect. When remissions occur they usually seem to do so spontaneously.

In summary, it may again be emphasized that acute disseminated lupus erythematosus is a systemic disease of unknown cause, with extensive and polymorphic cutaneous and visceral lesions apparently due to widespread vascular damage. It occurs chiefly in young or middle aged white females, many of the subjects being abnormally light-sensitive. The prognosis is grave. The clinical picture, while variable, is nevertheless marked by certain prominent features which, in the presence of the skin lesions, should in most cases lead to a correct diagnosis. The occurrence of leukopenia and certain lesions of the renal glomeruli appear to be strikingly constant features. The disease is of importance to the internist and the general practitioner as well as to the dermatologist. By its early recognition and the avoidance of certain dangerous procedures, especially exposure to sun and ultraviolet light, serious or even fatal exacerbations may at times be prevented.

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THE AGING PROCESS: A MEDICAL–SOCIAL PROBLEM *

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"Now that the average length of human life is increased and there are more and more old people, a fact that marks the triumph of science and civilization, there is more need of studying them, just as in recent decades children have been studied, for medically, at least after the climacteric, they constitute a class in the community that is somewhat alien, its intrinsic nature but little known, and the services it was meant to render but little utilized."

G. STANLEY HALL,[1] in *Senescence.*

INTRODUCTION

THE desire for long life and a delay of the onset of senile changes is accepted as a normal and legitimate objective. Until recently, however, there has been little scientific concern for the factors contributing to human longevity. Indeed, the distinctive needs, somatic and psychic, have been practically unconsidered. The older the man, the more he must depend upon his own hygienic sagacity for health and long life. It has been said that physicians know little about old age and its problems. Certainly, Geriatrics has not received as systematic consideration and analysis as have the problems of Pediatrics.[2] While scholars have written of the philosophical aspects ever since, and even before Cicero wrote "De Senectute," [3] the scientific study of Geriatrics is of comparatively recent origin.

Alexis Carrel, a short time ago, made an appeal for the endowment of an institute, dedicated to the study of the aging process. At the present time,

* Delivered before the American College of Physicians, New York City, April 4, 1938.

one of the great philanthropic foundations is collecting the important data on the aging process, and several notable investigators are now directing their attention to the aging problem.[4] Not only should youth be served and conserved, but likewise the values of later life need be recognized, studied, and more completely utilized. The masses of mankind are notoriously improvident of the future and in mid life the decrepitude of old age appears remote and uncertain.

The onward march of medical science has controlled the ravages of the early years, permitting more and more individuals to attain maturity. And now, the chances of reaching the later years of life are better than ever before. Therefore, a consideration of the aging process as a medical, and from the broader point of view a social problem, is of practical importance.

The Increase in Life Expectancy

One of the triumphs of modern medicine is the marked increase in life expectancy. In the sixteenth century, an infant had a life expectancy of 21 years. In the seventeenth century, this had increased to 26 years. By the middle of the eighteenth century, it was 34 years, and in the latter part of the nineteenth century it had extended upward to 40 years. In 1930,[5] male infants had an expectancy of 60 to 65 years and females from 62 to 68 years.

Expectancy of life in foreign countries, in 1930:

	Males	Females
Denmark	60.9	62.6
Sweden	61.10	63.33
Holland	61.09	63.5
Norway	60.98	63.84
New Zealand	65.04	67.88

Expectancy of life in the United States, 1930:

Iowa	65.90
Kansas	66.06
Minnesota	65.22
Nebraska	65.82
North Dakota	65.95
Oklahoma	65.42
Oregon	65.45
South Dakota (males 64.38)	66.81
Washington	65.41
United States (males 59.31)	62.83
Negroes (all told)	49.53

It is reasonable to presume that gain in expectancy of life will continue in the future, although certainly, it will not be at such a rapid rate. By 1960, a boy may expect to live approximately 75 years, and a girl may reach 80 years or more. The explanation for this spectacular increase in life, for such it is, resides in the increase in knowledge of both bacterial and parasitic diseases, as well as a clearer understanding of human nutrition.

Control of such diseases as bubonic plague, the black death of the Middle Ages, yellow fever, diphtheria, small-pox, typhoid fever, whooping cough and measles, have saved millions of lives of little ones. On the other hand, there has been little, if any, increase in the number of centenarians.

The 1930 census in this country showed that there were 3,964 persons 100 or more years of age.[6] Of these, it was recorded that 2,647 were Negroes. This seems incredible but may be possible on the basis of a placid, even temperament and an indisposition to be influenced by the nervous drive of modern existence.

More people, however, do reach middle life than at any other time in the history of the world. Once having attained the later years, there is no significant increase in the life span.

Accidents and Longevity

A systematic study of the various forces that injure and destroy life, with a corresponding listing of known precautions to avoid them, should be one of the objectives in a consideration of the prolongation of life. The difficulty with this approach, as pointed out by Malisoff, is that the solutions recommended are likely to be quite superficial. The strength of this approach, however, resides in the fact that many superficial facts taken together, may amount to something after all.

The most common and readily remediable cause of interruption or cessation of human life is the large number of accidents which maim or destroy human form, either in the home, on the highway, or in the factory. According to insurance statistics, the amazing number of 104,000 persons died accidentally in the United States in 1937. This figure was 6 per cent below that for 1936, although, with the exception of that year's total, it was the country's highest for fatal accidents.

One of the surest ways to keep from growing old is apparently to get mixed up in the traffic jamboree. The following is a list of automobile fatalities from the years 1932 to 1937 inclusive[7]:

	Deaths from Accidents
1932	29,451
1933	31,363
1934	36,101
1935	36,369
1936	37,800
1937	39,700

These statistics are mentioned in passing merely to emphasize the large number involved, and to suggest that individual and social caution and regulation can readily reduce this number.

Communicable Diseases, Infections and Longevity

Less than a century ago, communicable diseases accounted for approximately 900 deaths per 100,000 population per year. In order of their fre-

quency as a cause of death, these diseases were: tuberculosis, pneumonia, scarlet-fever, typhoid, diphtheria, whooping cough, measles and small pox. Except for tuberculosis and pneumonia, all of the other infections have been almost entirely eliminated as factors of importance. Less than 4 per 100,000 population died of these other infections during 1936, whereas, in the years 1856 to 1865, they caused on an average, over 300 deaths per 100,000 per year.[8] Preventive medicine is assuming a position of greater and greater importance in the medical-social sphere.

In the years 1856 to 1865, the average death rate from tuberculosis was 446 per 100,000 population, whereas in recent years it has averaged around 40 per 100,000 population—a decrease of more than 90 per cent. With a better understanding of the epidemiology and social and individual factors involved in the spread of tuberculosis, and a more enlightened policy on the part of the communities, tuberculosis as a cause of death will rapidly recede in importance.

Pneumonia had an average death rate of 107 per 100,000 population for the decade 1856 to 1865. In 1936, it was 96 per 100,000 population, representing a decrease of only 10 per cent. Today, however, pneumonia is more clearly understood, so far as its etiology, epidemiology, diagnosis and treatment are concerned. It is susceptible to control on a broad, geographical plan. Early diagnosis and adequate treatment, using the methods clearly understood and available today, should, in a relatively short span of years, remove pneumonia from its exalted position as third among the scourges of life in this country.

Medical science is progressing in such rapid strides, that bacterial and parasitic diseases will soon be eliminated as factors of importance which have heretofore interfered with, and too often interrupted the aging process, or the life span, of individuals. Special programs organized on a national scale, and energetically carried out by the medical profession, will go far towards controlling diseases such as syphilis and similar infections.

With the health of the people regarded as an interest of the government —Federal, State and Municipal—it is to be looked for and indeed hoped for, that in the not far distant future Departments of Health will have properly and adequately trained executives and personnel, persons educated in the broad field of public health, rather than appointees selected in a haphazard and random fashion. This move would seem necessary in any plan for adequate medical care for the nation.

The Degenerative Disorders

Once having reached middle age, the individual enters the age period when the so-called degenerative diseases, that is to say, disturbances of the heart and vascular system, high blood pressure, kidney disease, cerebral hemorrhage and diabetes appear on the horizon. These hazards of life assume an importance hitherto unconsidered because of the greater number of individuals in that age period.

The problems of middle and later life are somewhat different from those of infancy and childhood, medically speaking. They have to do more or less with the resiliency and stamina and elasticity of body tissues and organs, their hereditary background and predispositions.[9] The effects of the various stresses and strains of modern living conditions need to be kept in mind. Tissue resistance and repair must be studied from the chemical and physical approaches.

The wear and tear, the stresses and strains of existence need be analyzed, particularly along the lines that Bok has instituted in the study of personal problems of Harvard students. The effects of repeated acute toxic conditions, as well as low grade chronic infectious disorders, constipation and metabolic inadequacy need clarification.

With the decline in the birth rate, and at the same time an increase in the number of individuals living to mature and later years, the character of the national population is being slowly modified. The temper of the people is bound to assert itself in certain important changes which will extend into all the various phases of social, economic, political and professional life. A more mature national mind should have a steadying influence on the life of the nation.

From these observations it will readily be seen that the problem of aging is one of major dimension, and the diseases of middle and later life need to be more intensively studied than ever before.

Metabolic Disorders and the Aging Process

The two metabolic diseases which are most likely to interfere with the aging of the individual are obesity and diabetes. The overweight individual renders himself susceptible to a variety of disorders of the cardiovascular, gastrointestinal and other systems of the body, and in addition, is regarded as a poor risk by insurance companies. By restraint and wholesome living these individuals can add years to their life span.

Diabetes is rapidly on the increase. It has been estimated that there are more than one million diabetic patients in the United States, and that over a million more are susceptible to the disease.[10] Diabetes is important from the hereditary approach and as such, is a medical-social problem. Diabetics should not marry diabetics.

Investigations of the diabetic state have yielded important information regarding the process of arterial degeneration, notably one kind of arteriosclerosis. Uncontrolled diabetics, and particularly those on a high fat diet, are prone to develop hardening of the arteries early.[11] Likewise, they are more susceptible to coronary disease. These are problems of tissue degeneration.

Arteriosclerosis. Whatever the cause, sclerosis of the vascular system is certainly a form of tissue degeneration. Deposition of calcium in the injured tissues is probably a protective mechanism to safeguard the strength of the degenerated tissues. As such, it is a beneficent action of nature.

The work of T. Leary [12] strongly suggests metabolic deterioration as an important factor. A multiplicity of factors must be involved in the causation and, whereas the end result may be the same, a variety of influences in the nature of stresses and strains, or metabolic dysfunction, all based on a susceptible hereditary type of tissue, may explain the occurrence. No single set of experiments has been absolutely convincing. Nor is arteriosclerosis an affection of modern man, because in numerous instances sclerosis of the arterial system has been demonstrated in mummies, both of animals and man. The problem awaits solution. When the answer is found, life will certainly be further prolonged.

Nutrition and Longevity

Nutrition plays a part of equal, if not greater, importance than heredity in the development of a more vigorous body resistance and an extension of the span of years, according to Sherman. From experiments carried on over a long period of years on lower animals fed various types of diets, and from additional observations on human longevity, Sherman believes that, with the addition of generous portions of foods rich in calcium and vitamins A and G, six or more years of active life may be added to the prime years of human existence.[13] So convinced is he of this fact that he has governed his own diet accordingly. Apparently, certain factors can extend youth and increase vitality and the life span. Experimentally, it has been shown that a higher than average calcium intake is conducive to better than average health. With a calcium rich diet, there is an improvement in the utilization of food, better growth, greater adult vitality, a longer period between the attainment of maturity and the onset of senility, and, to a certain extent, an increase in the length of life. These observations were made on white rats, whose metabolism closely resembles that of the human being. The life span of man is approximately 30 times that of the albino rat, and the results are, of course, more rapidly obtained in the rat.

There is an important difference between an optimum diet and a merely adequate diet. An adequate diet, with the addition of certain important ingredients, will result in enhancement of nutritional well-being.

Sherman is of the opinion that, while the average American intake of calories is adequate, in the accepted sense, it is below that from which optimal well-being is to be expected. Foods rich in calcium such as milk, cheese, clam, eggs, vegetables, particularly beets, turnips, broccoli, cauliflower, bean, almonds and molasses, furnish a generous variety. As a problem of medical-social importance, Sherman believes that one-fifth of the food budget should be spent for milk and cream, not less than one-fifth for fresh fruit and green vegetables, and the remaining three-fifths for bread, butter, fish and eggs. Protective foods furnish propulsion power to the vital essence of existence and neutralize, at least partially, the degenerating forces within the body. By applying known facts regarding proper diet, the average life

span could be increased at least 10 per cent. Not only would years be added to life, but greater happiness, health and vigor result.

Hopkins maintains that faulty nutrition has played a large part in inhibiting human progress and he has observed that few races have been ideally nourished at any time. And according to Minot, man's place in future history will depend in no small part on diet.[14]

A scientifically planned diet will delay the onset of the ravages of old age. As whole milk is the ideal food for first childhood, so it can be accepted as the best single food for old age. As there is frequently a tendency towards development of a mild anemia in the later years, the use of liver twice weekly and iron rich foods will tend to maintain the level of the blood. For sluggish digestive powers and gastric atony, vitamin B_1 is frequently of value.

The nutritional requirements of older persons are less per kilo of body weight, but it is important that the specific foods, particularly such proteins as are contained in liver, and the vitamin B_1 complex and iron, be included in the diet. Likewise, a minimum fat content will protect the individuals from overweight where such a possibility exists. Much can be done with diet.

Normal and Abnormal Growth

A Consideration of the Nature of Cancer. The complex problem of cellular growth needs to be clarified. In order to understand more clearly the processes of body metabolism and aging, it will be necessary to study intensively the physical-chemical balance and existence of the individual cells which, in their aggregate, make up the human organism. Orderly growth of cells gives a healthy, normal human body. Disorderly growth with cellular expansion is cancer. This disorder destroys over 130,000 individuals each year in the United States.

The fundamental issues involved in a study of normal and abnormal growth, cellular and organized, when properly understood, will furnish knowledge which will prove invaluable for the development of a more hardy and rugged human species.

Cancer is a growth; as such it should be studied. The growth characteristics of cancer are two, namely, an increase in cell number which is unusual for the site and the age, and secondly, an incompleteness in differentiation or cell maturity. Whether the immaturity is secondary to the unwonted proliferation, or the unwonted proliferation is secondary to the cellular immaturity, or whether the two distortions have separate bases is of no immediate practical importance.

What is of practical importance is the validity of the following statement, namely, "The malignant character of cancer should be diminished by retardation of its proliferation and forwarding of its differentiation activity." As Hammett has stated, the best agents to bring proliferation toward its completion, should be those which Nature itself uses for these

ends. In the naturally occurring tissue components of general distribution should be found those agents which Nature uses for the regulation of proliferation and differentiation, and hence, those natural agents which should assist in bringing cancerous growths to relative innocuity.

Proliferation of cells is regulated among other chemicals by the naturally occurring specific and essential chemical equilibrium comprised in the sulfhydryl group and its sub-oxidized derivatives. This has been used by Hammett to produce for the first time a retardation of proliferative growth in spontaneous mouse tumors in a way used by Nature to bring normal increase in cell number to its natural end.

Using comparatively simple forms of cellular life, Hammett [15] has shown that each naturally occurring tissue component of general distribution has its own separate and peculiar influence on growth. The further observations of Hammett and Reimann [16] point to the probability that growth activity is significantly favored by some pyrrole derivative, possibly the pyrrolidone configuration or some part or derivative thereof. It has been proved that differentiation is advanced in the presence of compounds which are potentially interrelated through the pyrrole grouping and in the presence of no other compounds. The pyrrole influence may be traced through such chemicals as dextro-glutamic acid, laevo-aspartic acid, laevo-tyrosine, laevo-proline, and laevo-hydroxy-proline of the amino acids, and thymine and cystosine of the nucleic acid derivatives. These chemicals have the important function of forwarding differentiation. The pyrrolidone configuration is apparently an essential substance in the completion of cell maturity. As such, its importance in the study of cancer cannot be underestimated.

If it can be found what nature uses to bring cell multiplication to an end in the natural course of events, and if it is possible to find what Nature uses to make young cells grow up, then possibly one may be able to retard cell increase in cancer and force cancer cells to mature. In this way, the tumor would no longer be a cancer and life would be prolonged.

This work just cited is highly important and suggestive. The dynamics of normal and abnormal cellular vitality must be thoroughly investigated and understood before the cause of cancer will be finally known. The coordinated efforts of investigators with assistants from various special fields as biology, physiology, physical chemistry, mathematics, statistics, etc., will solve the problem eventually.

For the carrying on of this important work public support is essential. Recently, generous funds have been made available by private philanthropies for just such work. In addition, the United States government has signified its recognition of the importance of the work. Brains are more important than buildings and funds should be utilized for the conduct of a long range plan of approach to the problem. Small grants for small-time work are not very helpful.[17]

Meanwhile, the public may help in the battle against cancer by keeping informed of the developments, and by health examinations at stated inter-

vals, particularly, of all individuals over the age of forty-five. Small growths or chronic sores, or warts and moles or discharges which have persisted, should be recognized and eliminated before they have developed to the cancerous state.

Rejuvenescence

The hope for recapture of youthful vigor and enthusiasm, particularly in the erotic life of the individual, has been expressed by numerous observers, and has been the object of innumerable pseudoscientific investigations and treaties. Latterly, Voronoff and his followers have claimed spectacular results from testicular glandular transplants, and Steinach has advocated the severance of one or more of the glandular ducts. Extravagant claims have been made for these procedures. Numerous cases have been cited, wherein sexual power has been regained and the ability to participate in the sexual act has been described.

Such an approach to the problem of prolongation of vitality places an undeserved emphasis on the single force of sexual activity. Even were it possible to reawaken the somnolent sex life of the individual and revitalize the function and structure of the genital tract, the unwisdom of such a procedure would soon become manifest. Other vital systems, and more particularly the cardiovascular tract, central nervous system, and the muscular equipment of the body, play a more dominant rôle in the health and welfare of the elderly individual than does the genital tract. Rejuvenescence of all the tissues of the body has to date not been accomplished.

Industry and Forty-Phobia

With more individuals attaining the middle years of life, and, at the same time, in better physical, nervous and mental condition than at any previous time, the value of their labor ability and contribution to society requires broader recognition. While physical maturity is more exuberantly evident in the early years of adult life, emotional maturity and with it, stability, comes relatively later. An individual is at his best when maturity of the physical, intellectual and emotional patterns have attained their full stature. This is probably somewhere between the years of forty and sixty. Therefore, it should be realized that persons from forty on, most likely bring to their work the factors that make them most useful. Mature individuals in the middle years are less restless, have a better appreciation of values, have more experience, have an understanding of proportion impossible in youthful adults, and are likely to be more valuably productive.

A recent survey of some of the country's largest industries, which report was made to the Sales Executive Club in New York, indicated that individuals over forty are more conscientious than those under forty, that they are more open-minded toward criticism, that they undertake unpleasant tasks more willingly, and finally, bring in more new ideas of value.

The attributes credited to young men such as enthusiasm and cheerfulness, prompt adaptability, more attention to personal appearance, and promptitude in developing a new assignment are equally applicable or possible to individuals of more mature age.

A recent study of 1,444 skilled workers on WPA projects,[18] showed that those receiving higher grades for quality of work were also in the higher age brackets. The average age of those workers graded as excellent was 47 years and the average of those counted inferior was 41 years. The survey further indicated that older men produce more than younger men at any set task. It is encouraging to note that the average age of automobile workers is rising and in more and more divisions the tendency is to give preference to men over forty, particularly for the handling of multiple machines.

In a challenging article recently, Waldemar Kaempffert has discussed "The Man Over Forty: A Machine Age Dilemma."[19] Kaempffert cites four charges that industry has made against the man over forty.

First, that he is a bad physical risk. It is said that, over forty, a man enters the period of life when the degenerative diseases will lower his efficiency or incapacitate him entirely. Certainly, there is a relation between occupation and health and longevity, which industry does not take into account. The highest death rate occurs among the unskilled and semi-skilled callings. When individuals falling in these occupation groups are favored with the benefits that modern science has to offer toward a more vigorous and prolonged existence, and when industry improves the conditions under which such laborers carry on, it will be found that the death rate can be substantially reduced. The man over forty is not of necessity a bad physical risk.

The second charge is that of lowered productivity; but recent measurements, as pointed out, have indicated that the period of greatest productivity may lie somewhere between 47 and 60 years, so that this charge can be substantially refuted today. There is strong physiological and psychological evidence that many men are just as proficient at 50 or 60, or even more so, than their younger competitors. As the benefits of science in the form of nutrition and a more intelligent, personal hygiene are extended to large groups of workers, and conditions under which they labor are improved, their productivity will certainly increase.

Third, it is said that individuals above 40 years of age are bad accident risks. But here, as Kaempffert has emphasized, this attitude of industry is definitely in error. To prove his point, he cites a survey which differentiated between jobs held by the young and the old, as studied by the British Industrial Health Research Board. This Board found that the man over 40 was more careful and conscientious than his younger competitor. Age and experience have definite dividends to offer. The British findings are likewise confirmed in a study of 65 manufacturing plants and four railroad repair shops in the state of New York.

The fourth charge is that men above 40 are too slow and unadaptable to

changing conditions. Then again, the same statement concerning the benefits of improved personal hygiene and scientific nutrition and better working hours and better working conditions, will tend to make the man over 40 practically as adaptable as the one under forty.

In a day when overproduction is the rule, high pressure methods whereby still more goods may be produced or manufactured are definitely unnecessary. American industry has too frequently driven its masses of men at a feverish pace, to their detriment. A marked deceleration of this pace would contribute immeasurably to the nation's peace of mind and health of body.

At the present time, 260 out of every 1,000 persons living in the United States are 40 years or over in age. By 1960, statisticians estimate that 36 per cent of the population will be between the ages of 40 to 65 years. With more and more able bodied individuals at mature age levels, the need for new industries together with a more profitable use of leisure carry new meaning.

The Retirement Problem

The practice of retiring individuals after a certain age limit has been reached, is widespread in business, industry and the professions. Labor organizations have long been in favor of the retirement age, at which time a worker is placed on pension. One of the major benefits derived from this principle is the creation of enlarging opportunities for younger men on their way up, by the creation of openings in positions of responsibility.

With the increasing span of useful life, particularly in lengthening of the productive years, large numbers of individuals, both men and women, will be displaced at a period in their lives when their individual productivity has not been diminished. And in those individuals whose physical stamina is lessened, there yet remains the important factor of experience which is always an asset. This is a problem of growing importance today.

The resourceful individual always has a multiplicity of interests and enthusiasm that challenge his energy and time allotment. Retirement for this individual means but the transference of interest from one activity to another.

It is difficult to designate a year age at which time those engaged in any specific work should be relieved of further responsibility, since the vitality and ability to carry on is an entirely personal matter.[20] With a clearer appreciation of scientific nutrition and improved methods under which man labors, his period of productive maturity should extend into the later years of life. Furthermore, it has been generally recognized that individuals possess a generous physical and nervous reserve which is rarely utilized.

Retirement too often for the individual means rust as well as rest. The profitable use of leisure determines the fullness and value of the later years, particularly of that period subsequent to retirement.

Social Implications of Longer Life

With more effective control of life-destroying degenerations, malignancies, infections, deficiencies and traumas, the life span of man is going to be lengthened and the mature and productive years will be more in number and, it is to be hoped, the senile period will be reduced to a shorter time.

Labor-saving devices together with improved conditions and sanitation for workers, and more hours of leisure for the laboring class, help to preserve the vital essence of the living process and prevent the body from aging faster than the mind.

As living conditions and the various details of human existence improve more persons reach old age and, therefore, their futures need be reckoned with. Today, little, if anything, is done to fit individuals for old age, and they reach it unprepared and uninformed. The dearth of knowledge concerning the needs of the aged has been repeatedly emphasized by Carrel,[21] Sherman, Pearl and others. An intelligent and well-conserved senectitude has important social and anthropological functions.

Hall [22] points out that present day society is characterized by distracting specializations of work and interests. The synthesis of social existence, that is, the unification of the various integrated streams of human interest, can best be accomplished by mature individuals with adequate years of experience and an appreciation of life as a whole.

New problems of medical-social value loom in the foreground. The conquest of the unknown has gone forward at an incredible rate. New methods and disciplines are being developed. Cannon has pointed out that the hardest tasks confronting the medical profession are those related to the nature of man and the factors which determine his conduct.[23] It is the inhumanity of human beings that spoils the achievements of science. As major disorders of the intellect and personality are now under scientific scrutiny and not infrequently responding to beneficent treatment, other inhuman traits such as cruelty and belligerency may be considered within the realm of medical accessibility.

Cannon asks, " What can be done to improve human behavior? " And he states, " Here, one confronts the most important frontier of all." The problem of human motivation becomes a medical-social challenge. Cannon points out that potent biological factors which shape the ends of men are now known that have heretofore never been dreamed of. And recently, investigators using methods which proved effective in the past have begun to unravel and evaluate the strength of some of the forces which play an important rôle in determining what man is and what activates him.

The cretinous idiot can be transformed into a child with normal intelligence. The patient with schizophrenia but recently has responded to treatment. The powerful forces which shape man and his destiny and which exist within him are now being subjected to the intensest kind of scientific analysis. A great and as yet uncharted realm of profound medical and social significance awaits exploration.

The revolution which is reshaping medical science is not merely a fight against death, but also, a fight for life with all the implications, both economic and social, which emerge from science's successful lengthening of the life span, as Gray has so ably described.[24] The society which fosters research to save human life cannot escape responsibility for the life thus extended. It is for science not only to add years to life, but more important, to add life to the years.

In the words of Charles E. Merriam, "If the devices of social invention are able to keep pace with the scientific organization of nature, the new road may lead to a fairyland of achievement." [25] The burdens of hunger, disease, toil and fear may be listed. Leisure and the treasures of human appreciation and enjoyment may be available to all mankind. The diseases of intolerance and the lust to kill may respond to treatment just as some of the other mental diseases heretofore regarded as incurable.

What group of society is qualified by training, experience, and broad interest to investigate these problems of vital importance to the world today if it is not the medical profession? Industry, government and church have their varied and justifiable interests in other aspects of the individual. The medical profession alone studies him from the somatic, nervous, intellectual, and emotional approaches, learns his assets and his liabilities and endeavors to help him to take his position in the social plan.

An intensive consideration of the aging process is bound to lead to worthwhile data. From the facts thus obtained, individual existence should be enriched, which, after all, is about as good an objective as any towards which the medical profession can direct its interests.

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A CLINICAL STUDY OF MALIGNANT HYPERTENSION *

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PHYSICIANS have long recognized that the clinical course of arterial hypertension is exceptionally variable. The lives of some patients appear to be little shortened by elevated blood pressure while others succumb within periods measurable in months. Volhard and Fahr (1914) emphasized these differences by the terms "benign" and "malignant," and Volhard pointed out that the benign form of hypertension may at any time turn malignant.

For some years the genesis of hypertension which showed signs of a rapidly fatal outcome was ascribed to the kidneys. Scant regard was paid the blood vessels in the remainder of the body. The morbid state was variously called "malignant nephrosclerosis" or "genuine contracted kidney." Fahr (1919), Volhard (1918), Fishberg and Oppenheimer (1930), and Wagener (1930) later demonstrated that the lesions were not limited to the kidneys and that retinal change is the earliest observable sign.

Keith, Wagener, and Kernohan (1928) presented a classic description of 81 patients of arterial hypertension with characteristic retinitis, adequate renal function, and rapidly fatal outcome. Less importance was attached by them to the part played by the kidneys in the genesis of the syndrome. The ubiquity of the arterial damage was stressed. They termed this type of hypertension the "syndrome of malignant hypertension." These observations were shortly confirmed and extended by very careful studies of Murphy and Grill (1930). Ellis (1932) has published one example of each of four clinical types of malignant hypertension—cerebral, cardiac, renal, and combined. Observations on the clinical course of malignant hypertension which agree closely with those in this paper have just appeared from the pen of Arthur Ellis (1938).

The origin of the syndrome of malignant hypertension is obscure. Volhard, in particular, believes that the kidneys participate in its genesis. Its occurrence, superimposed on essential hypertension, suggests that it might be the result of acceleration of the mechanism responsible for the latter. This theory is as yet without objective support. Derow and Altschule (1935) believe it to be of multiple etiology.

Klemperer and Otani (1931) have ably summarized the literature concerning "malignant nephrosclerosis." Suffice it to say here that the clinical signs and symptoms of malignant hypertension may occur both with and without evidence of severe renal damage as determined by contemporary laboratory methods. But this does not prove that the kidneys are not involved in the genesis of the clinical syndrome of malignant hypertension.

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A disease closely resembling malignant hypertension has been produced in dogs by tight clamping of the main renal arteries by Goldblatt (1938). Renal insufficiency appeared to be an essential factor in its development. Necrotic arterioles and hemorrhages were not observed in animals that had very high blood pressures for years without renal insufficiency, nor in animals with azotemia due to removal of both kidneys, but without hypertension. Ischemia was not the cause of the arteriolar necrosis because it was absent in dogs' kidneys made ischemic and widespread in other organs that were not ischemic. The necrotic arterioles and hemorrhages were secondary to and not the primary cause of this type of malignant hypertension.

The author can confirm Goldblatt's observation, for five examples of malignant hypertension have been observed which correspond in most details to his convincing description of the syndrome. Especially impressive were the changes in the eyegrounds which consisted of intense arteriolar constriction, arteriovenous compression, sclerosis, hemorrhage, exudate, papilledema, detachment of the retina, and blindness, just as observed by Keyes and Goldblatt (1937).

Most clinicians agree that malignant hypertension may be engrafted upon essential hypertension. Such cases are common and will be omitted from the records of patients presented in this communication. Hypertension appears to have been malignant from the onset in our 30 patients. Since these patients were followed in the Hospital of the Rockefeller Institute at intervals for periods up to seven years, it was believed of interest to present pertinent observations from their records.

Methods

Renal efficiency was measured by urea clearance and ability of the kidneys to concentrate urine. Urea clearance was employed not only because it is a most delicate test but because Van Slyke, Rhoads, Hiller and Alving (1934) have shown that in dogs it parallels the renal blood flow. The specific gravity was measured of a twelve-hour specimen voided at the end of 24 hours without fluids. If protein was present in sufficient amount to contribute to the specific gravity, a correction was made for it; that is, 0.003 was subtracted from the total specific gravity for each 1 per cent of protein. The number of formed elements in the urine was estimated by the technic of Addis (1926). Not more than 500,000 red blood cells are excreted by a person with normal kidneys. The protein content of the urine was measured by the method of Shevky and Stafford, as slightly modified by MacKay (1932). The protein content of the plasma was ascertained by the method of Howe (1921), and the hemoglobin content was measured by the Van Slyke and Neill oxygen capacity method (1924).

Explanation of the Charts. On the charts the mean normal of each measurement represented is drawn as a base line; the shaded areas between the base line and the points representing observations indicate the degree of deviation above or below the average normal. The brackets at the left of

the scales for urea clearance, concentration of urine, and hematuria indicate the range of normal variability. The normal base line for the hemoglobin value varies with the patient's age and sex. Measurements of the blood pressure were made daily at 9:30 A.M., *but are represented in the charts as averages.* Morbid changes in the eyegrounds are recorded as follows: (1) constriction of the arterioles, (2) arteriosclerosis, (3) exudate, (4) hemorrhages and (5) papilledema. The estimated time which elapsed between the onset of the disease and the patient's admission to the hospital is recorded on the lowest line of the chart as the first number following the word "months." The other numbers in the bottom row indicate months after patient's first admission to the hospital.

Results of Study of Patients

Thirty patients were studied (table 1). Nineteen of these were males and 11 females, varying in age from 14 to 48 years (average 33 years). Of these, 24 are dead, 5 alive and 1 patient was not followed. Six patients were subjected to the operation of anterior spinal nerve root section and have been described in a previous communication (Page and Heuer, 1937). Three of these (Nos. 2, 13, 18) are alive and 3 dead (Nos. 4, 5, 12). Supradiaphragmatic splanchnic nerve section was performed on three patients (Nos. 1, 3, 30) and all are dead (see Page and Heuer, 1937).

The chief complaints in order of their frequency were headache (13 patients), visual disturbance (7 patients), fatigue (4 patients), dyspnea (2 patients), convulsions (1 patient), fainting (1 patient), weakness (1 patient), precordial discomfort (1 patient), and edema of ankles (1 patient). One-third of the patients stated that high blood pressure occurred in their families, but in only five was this definite enough to suggest that it may have had a bearing on the patient's illness. It is of interest that seven patients had had scarlet fever and one chorea. The past history of the remainder did not appear significant.

Since the high-strung, neurotic temperament is commonly observed in patients suffering from essential hypertension, it was considered of interest to observe whether similar primitive emotional behavior was present in those with the syndrome of malignant hypertension. Twenty of the 30 patients were classified as being emotionally unstable, but only 11 were definitely so. Few of them exhibited signs such as blushing and crying, part of the "hypertensive diencephalic syndrome" (so-called because of its resemblance to the signs and symptoms which follow stimulation of centers in the diencephalon (Page, 1935)), which may often be associated with cases of essential hypertension.

The feeling of fatigue was very common, occurring in all but nine patients. In spite of this, it was the chief complaint in only four of them. Except for dyspnea on exertion, which occurred in 21 patients, other signs or symptoms referable to the heart were rare. "Cardiac" pain was experienced in five patients and palpitations in twelve. Palpitations were

TABLE I

Incidence of Signs and Symptoms in 30 Cases of Malignant Hypertension

Case No.	Sex	Age	Duration of Disease from Onset to Death (in Months)	Chief Complaint	Family History	Past History	Temper-ament	Fatigue
1	M.	48	9	Weakness	0	Scarlet Fr. 2 yrs.	+	+++
2	M.	44	Alive (Ant. root sec.)	Weakness and failing vision	+++	0	+	0
3	F.	18	29 (Splanchnic sec.)	Headache	0	0	0	0
4	M.	43	18 (Ant. root sec.)	Blurred vision	++	Scarlet Fr. 18 yrs.	++	+++
5	M.	26	14 (Ant. root sec.)	Blindness rt. eye	0	0	0	+
6	M.	14	25	Convulsions	0	0	0	+
7	M.	40	40	Headache	0	0	0	0
8	M.	25	28	Headache	0	0	0	++
9	M.	46	71	Dyspnea	+	Scarlet Fr. 8 yrs.	+	+
10	M.	37	Alive	Headache	+	Scarlet Fr. 29 yrs.	+	+
11	M.	24	58	Fainting	0	0	0	0
12	M.	37	48 (Ant. root sec.)	Headache	0	0	+	0
13	M.	24	Alive (Ant. root sec.)	Blurred vision	0	0	0	0
14	F.	36	78	Blindness	0	0	++	0
15	F.	21	19	Fatigue	0	Scarlet Fr. 7 yrs.	+++	++++
16	M.	25	81 (Splanchnic sec.)	Headache	0	0	+++	+++
17	F.	45	—	Blindness	0	0	++	+
18	F.	21	Alive (Ant. root sec.)	Headache	0	Scarlet Fr. 10 yrs.	0	++
19	F.	39	19	Dyspnea	0	0	+++	+++
20	M.	48	20	Precordial discomfort	0	0	++	++
21	F.	34		Headache	0	Scarlet Fr. 8 yrs.	0	+++
22	M.	37		Headache	++	0	++++	+
23	M.	48		Headache	0	0	++	++
24	F.	33	About 4 years	Fatigability	++	0	++	+++
25	F.	33	54	Edema of ankles	++	0	+	++
26	M.	24	37	Failing vision	0	0	0	0
27	M.	40	64	Fatigability	0	0	+	++
28	F.	26	53	Headache	+	0	+	+++
29	F.	21	Alive	Blurred vision	+	Chorea 10 yrs.	+	0
30	M.	40	129	Headache and fatigue	+	0	++	++

TABLE I—*Continued*

Headache	Crying	Blushing	Palpitation	Cardiac pain	Dyspnea	Weight Loss	Nausea Vomiting	Nocturia	Cause of death
+	+	+	+	o	+	o	o	1	Uremia
++	++	o	++	o	+o	o	o	0	Alive
+++	o	o	o	+	+++	++	+	1–3	Uremia
+++++	o	o	o	o	+	++	++	1	Apoplexy
+	+	+	+	o	++	o	o	4	Uremia and cardiac
+	o	o	o	o	o	o	o	?	Uremia
++	+	o	o	o	++	+	+	o	Uremia and cardiac
+++	o	o	o	o	+	o	+	1	Uremia
+++	o	o	o	o	+	o	o	2	Cardiac failure
+++	o	o	o	o	o	o	o	0	Alive
+	o	o	o	o	+	o	o	1–2	No follow up
++	o	o	o	o	++	++	o	0	Cardiac failure
+++	o	o	o	o	+++	++	o	o	Alive
+++	o	o	+	o	+	+	o	o	Apoplexy
+++	o	+	o	+	++	+	o	o	Apoplexy
+++	o	++	+	o	+	+	o	++	Cardiac failure
+++	o	+++	o	o	o	o	o	+	Unknown
+++	o	++	+	o	o	o	o	o	Alive
+++	o	+++	o	o	+	o	o	1	Alive
+++	o	++	+	o	++	+	o	1–2	Cardiac failure
+++	o	+++	o	o	++	+	o	0	Alive
+++	o	++	+	o	o	+	+	2–3	Uremia?
+++	o	+	o	o	o	+	o	1–2	Alive
+++	o	o	o	+	+	+	+	5–6	Cardiac failure
+++	o	o	o	o	+	+	+	0	Cardiac failure
+++	o	o	o	o	+	+	+	6–12	Cardiac failure
+++	o	o	o	o	+	o	o	2–3	Uremia
+++	o	o	o	o	+	+	o	1–2	Uremia
+++	o	o	o	o	o	+	+	2–3	Uremia
+++	o	o	+	o	o	o	o	1	Alive
+++	+	o	+	o	+	+	+	0	Apoplexy

severe in three patients and caused them annoyance. The genito-urinary system also produced few symptoms. Nocturia occurred in 19 patients, but was troublesome in eight.

Nausea and vomiting were complained of by one-third of the patients. They were severe in only one. Weight loss, which was noted in 17 of the patients, was moderate in 15, and severe in 2.

The chief cause of death was difficult to ascertain in many of the patients because of concomitant failure of more than one organ. Uremia was believed to be the chief cause in ten patients, cardiac failure in seven, and apoplexy in four.

The results of laboratory examinations as well as certain pertinent data from physical examinations are given for most of the patients in the graphic charts. This enables one to follow the course of the disease without recourse to the many figures involved.

Renal function was measured by urea clearance and maximal ability to concentrate urine when the patient was admitted to the Rockefeller Hospital. Urea clearance was above 55 per cent of normal in 60 per cent of the patients, between 20 to 55 per cent in 27 per cent, and below 20 per cent in 13 per cent of the cases. The average time which had elapsed before the urea clearance was performed in the three groups was 31, 25, and 36 months after the estimated onset of the disease.

The maximal ability to concentrate urine was found between the normal limits of 1.024 to 1.031 in 21 per cent of the patients. It was reduced, i.e., 1.014 to 1.024, in 50 per cent and sharply reduced or lost, i.e., 1.008 to 1.014, in 29 per cent of the cases.

The hemoglobin as estimated by oxygen combining capacity and expressed in volumes per cent was found slightly above normal (21 to 23 volume per cent) in 14 per cent of the patients, normal (18 to 21 volume per cent) in 50 per cent, below normal (14 to 18 volume per cent) in 30 per cent, and sharply reduced (11 to 14 volume per cent) in 6 per cent. Plasma proteins were normal (6.8 to 7.8 gm. per 100 c.c.) in 58 per cent of the patients, slightly reduced (6.0 to 6.8) in 32 per cent and moderately reduced (5.4 to 6.0) in 10 per cent.

Morbid changes in the composition of the urine were for the most part slight. One-half (53 per cent) of the patients excreted less than a gram of protein in 12 hours, while 40 per cent excreted from 1 to 5 grams. The urine of only 7 per cent of the patients contained more than 5 grams of protein. The number of red blood cells in the urine was within normal limits in 64 per cent of the patients, exceeding these limits (from 1 to 5 million cells in 12 hours) in 16 per cent. Marked hematuria (5 to 20 million cells) occurred in 20 per cent.

Teleradiograms were made of the patients' hearts on admission to the hospital. The transverse diameter of the cardiac shadow was measured and compared with the internal diameter of the chest. The ratio, $\frac{\text{diameter of heart}}{\text{diameter of chest}}$, was below 55 per cent in 40 per cent of the cases (table 2).

TABLE II

Electrocardiographic and Roentgen-Ray Findings in Malignant Hypertension

Case No.	Electrocardiogram *						X-ray				
	T-waves Leads			A-V conduction time in seconds	Left axis deviation	Other changes	Of Heart		Diam. heart / Diam. chest	Of Skull	
	I	II	III				Total transverse diameter in cm.	Total internal chest diameter		Changes in sella	Pineal calcification
1	+	+	+	0.24	lad	$R_{1,2,3}$ split					
2	±	±	−	0.16		P_3 diphasic	13.2	29.0	46	+	+++
3	+	+	+	0.10	lad		10.2	23.5	44	+	0
4	+	−	−	0.17	lad	P_2 high	16.8	28.0	60	0	++
5	−	−	+	0.20	lad		17.2	27.4	62	0	0
6							11.0	23.5	47	0	0
7	−	+	+	0.14	lad						
8	+	+	±	0.14	lad		13.8	24.5	56	0	0
9	−	−	+	0.17	lad	$R_{1,2,3}$ split, Q_3					
10	−	+	+	0.16	lad	Q_3	13.8	26.0	53		
11	−	−	+	0.15	lad	$-P_3$	15.5	32.0	49	0	+
12	+	−	−	0.14	lad	$QRS_{2,3}$ split	13.2	27.7	48	0	++
13	+	+	−	0.17	lad	Q_3 [illegible]	13.1	26	50	0	0
14	−	+	+	0.17	lad	P_2 split	11.8	23.7	49		
15	−	+	+	0.14		$R_{1,3}$ split	14.4	21.2	68	0	0
16	±	+	±	0.19			14.6	26.8	54	0	+
17							13.7	23.0	59		
18	−	−	+	0.12	lad	$-P_3$	14.5	26.4	55	0	+
19	−	−	+	0.14	lad		14.6	25.6	57	walls thinned	0
20	−	−	+	0.19	lad		17.7	29.5	60	0	++
21											
22	−	−	+	0.12	lad	P_2 split	14.5	26.0	56	0	0
23	−	−	+	0.16	lad		18.1	28.8	63	0	+
24	−	−	+	0.16	lad		15.5	23.5	66	0	+
25	±	±	+	0.18	lad		19.7	23.9	82	0	+
26	−	±	+	0.16	lad		14.8	28.0	53	0	
27	+	−	−	0.16		Q_2	17.6	31.5	56		
28	±	+	+	0.17	lad	R_3 split					0
29	+	+	−	0.13			13.5	23.4	57	0	+
30	−	−	+	0.18	lad	P_3 diphasic	13.8	24.5	56		

* These electrocardiograms were taken by Miss M. Alleman through the courtesy of Dr. Alfred Cohn.

The remainder were above. In most patients enlargement of the heart was moderate. However, as the disease advanced enlargement was often, though not always, very rapid.

The electrocardiographic deviations from normal were often marked (table 2). Negative T-waves were observed in Lead I in 56 per cent of the patients, in Lead II in 50 per cent, and in Lead III in 25 per cent of the patients. The T-waves were isoelectric in Lead I in 14 per cent of the patients, in Lead II in 10 per cent of them, and in Lead III in 7 per cent of the patients. Preponderance of the left ventricle was noted in the majority (82 per cent) of patients. Other changes such as splitting of the QRS complex and negativity of the P-waves were only occasionally observed. The P–R interval was greater than normal (normal = 0.20 second) in only one patient (No. 1).

Stereo-roentgen photographs were made of the skulls of the patients (table 2). The only unusual finding was the frequent occurrence of calcification of the pineal gland. This was observed in 55 per cent of the cases. Ten per cent showed changes from normal in the sella, but they were not of sufficient grade to be considered significant. At autopsy of one of these patients nothing abnormal was found in the sella.

Examination of the ocular fundi showed extensive morbid changes in all patients. Particularly impressive was the intense constriction and tortuosity of the arterioles. In the eyegrounds of some of the patients the number of vessels appeared to have decreased markedly, only a few irregular ones remaining. In some the vessels were straightened. Arteriovenous compression was usual. The veins appeared large in comparison to the size of the arterioles, of abnormally dark color, and tortuous. Edema and detachment of the retina were common. Papilledema of marked degree was present in many cases. Exudate as well as hemorrhages were observed in all cases. In all but three of the patients who were not operated upon, these pathological signs became more extensive as death approached. These three, subjected to the operation of anterior nerve root section, exhibited marked regression of the fundus changes (Cases 2, 13, 18). This consisted of disappearance of hemorrhages, exudate, and papilledema in two cases (13, 18) and marked regression in the third (2). In seven of the patients partial or complete blindness occurred. Secondary glaucoma was observed in one patient. The tension in one eye was so great that it could not be registered by a Schiötz tonometer. After anterior nerve root section, the tension returned to normal (Case 18).

Nothing characteristic was observed about the blood pressure except its elevation. The systolic pressure was usually very high (230 to 260 mm. Hg), but by no means always (see Case 5). The diastolic pressure was rarely below 140 mm. Hg and the pulse pressure tended to be somewhat reduced (see Case 25 for example). The diastolic pressure rarely exhibited a tendency to fall (see Case 20) except during the terminal phase when cardiac failure supervened.

• These electrocardiograms were taken by Miss M. Alleman through the courtesy of Dr. Alfred Comm.

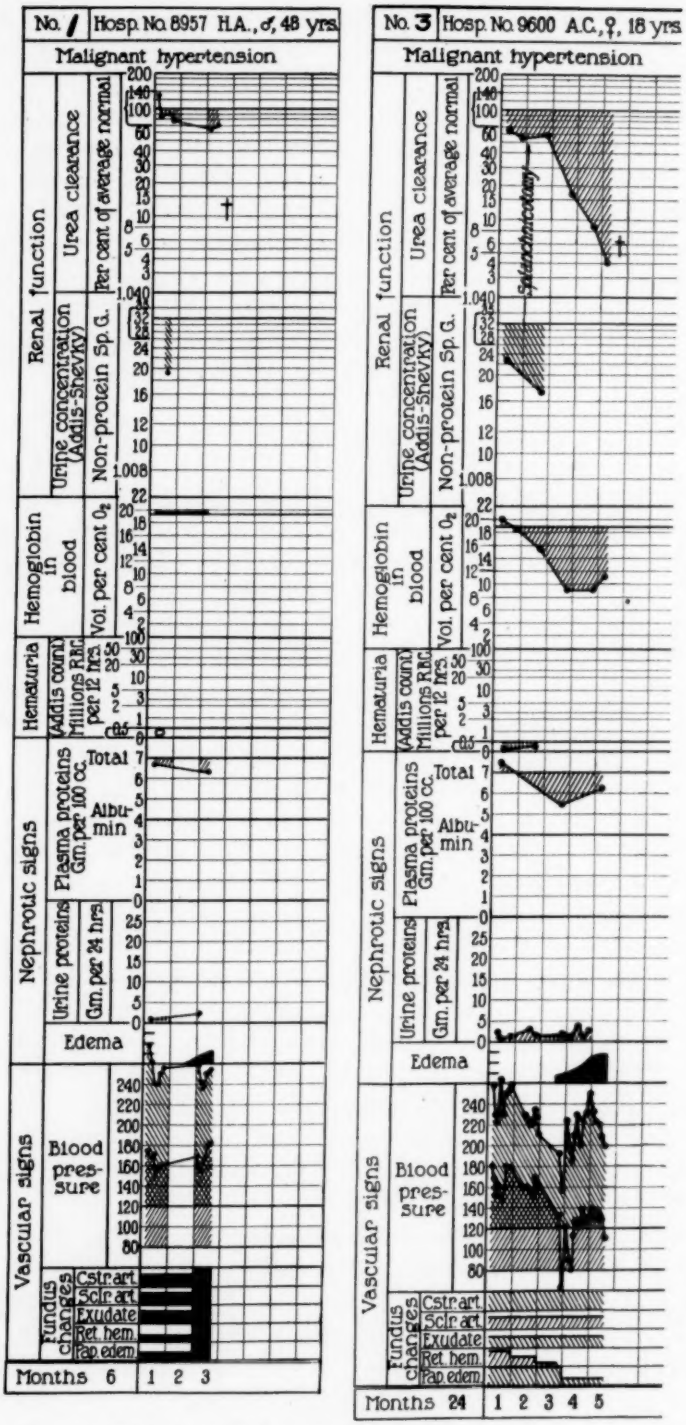

FIG. 1. Clinical and laboratory data depicting the course of malignant hypertension. Cases 1 and 3.

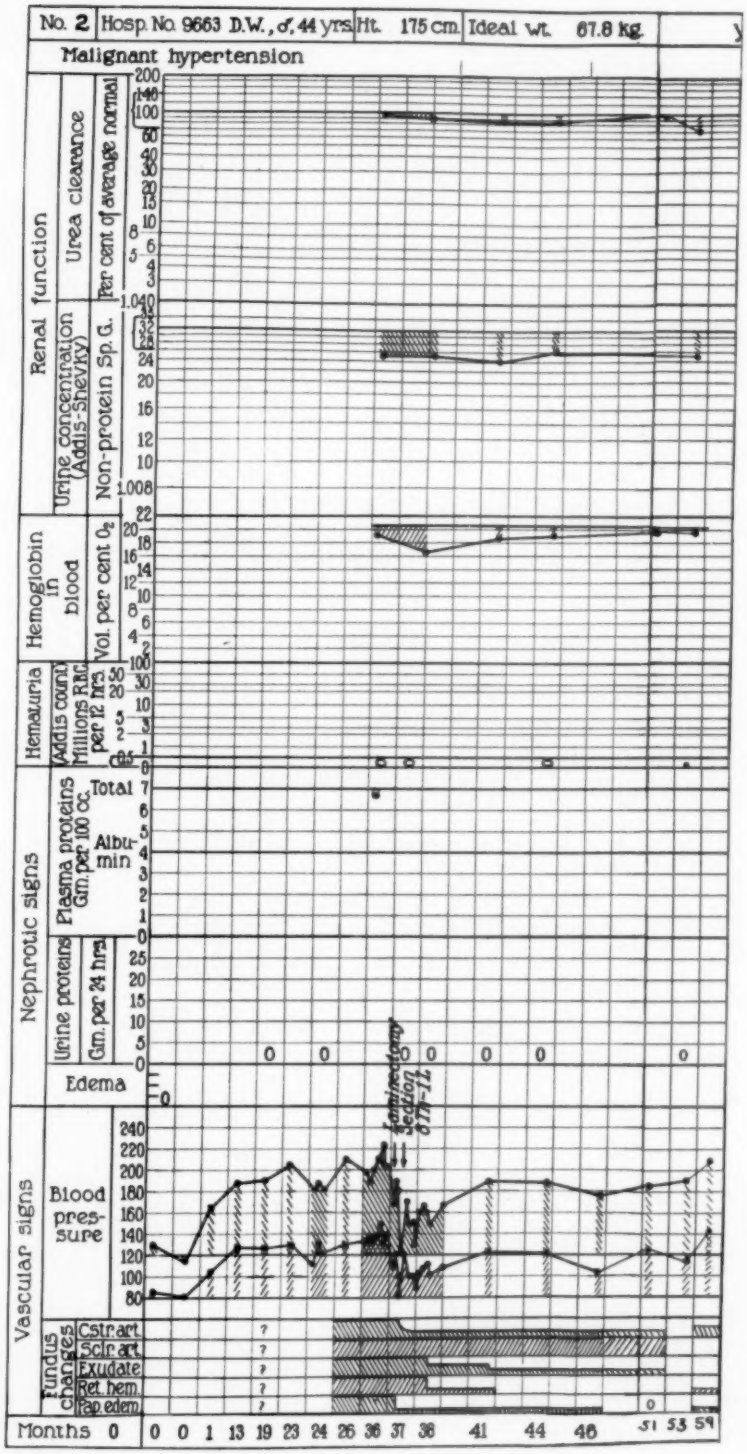

FIG. 2. Clinical and laboratory data depicting the course of malignant hypertension. Case 2.

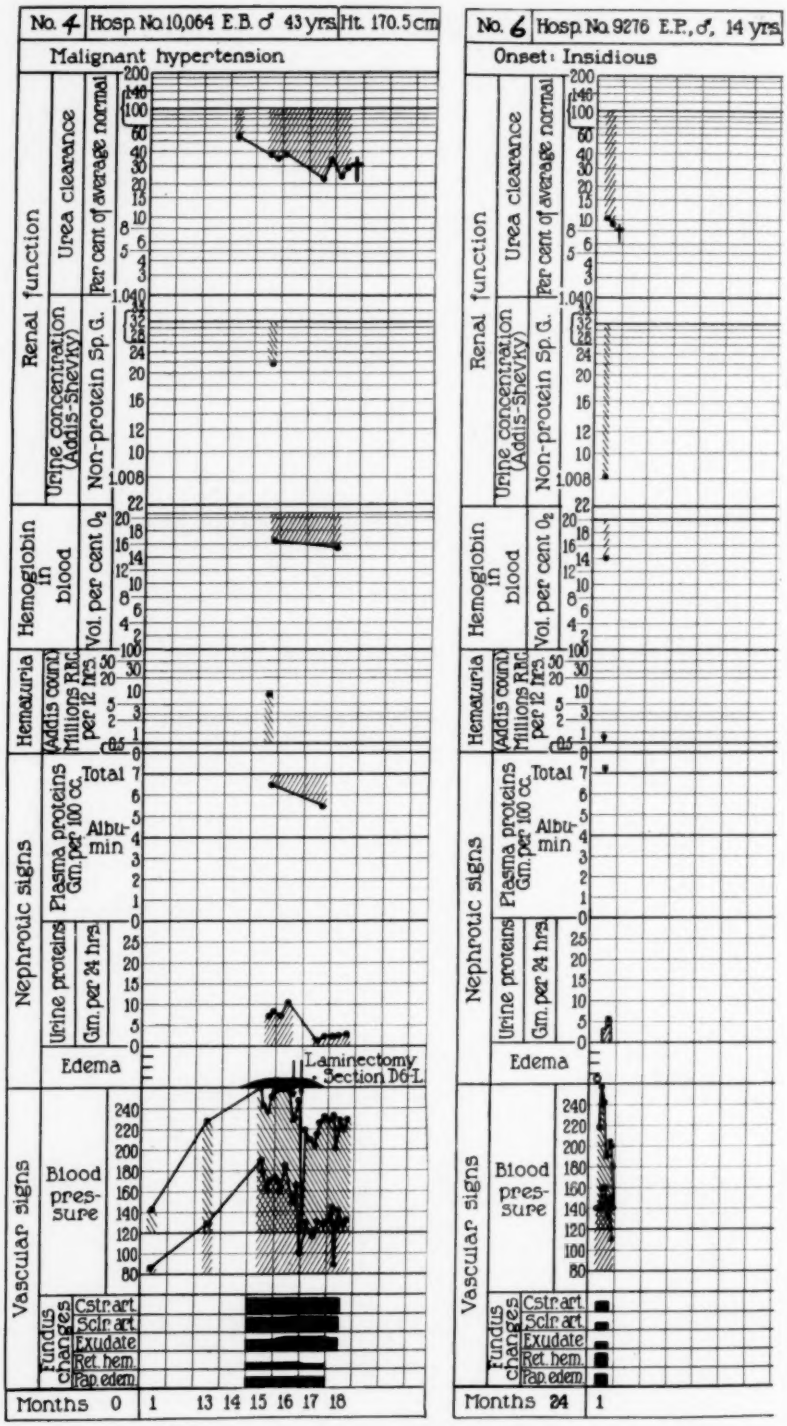

FIG. 3. Clinical and laboratory data depicting the course of malignant hypertension. Cases 4 and 6.

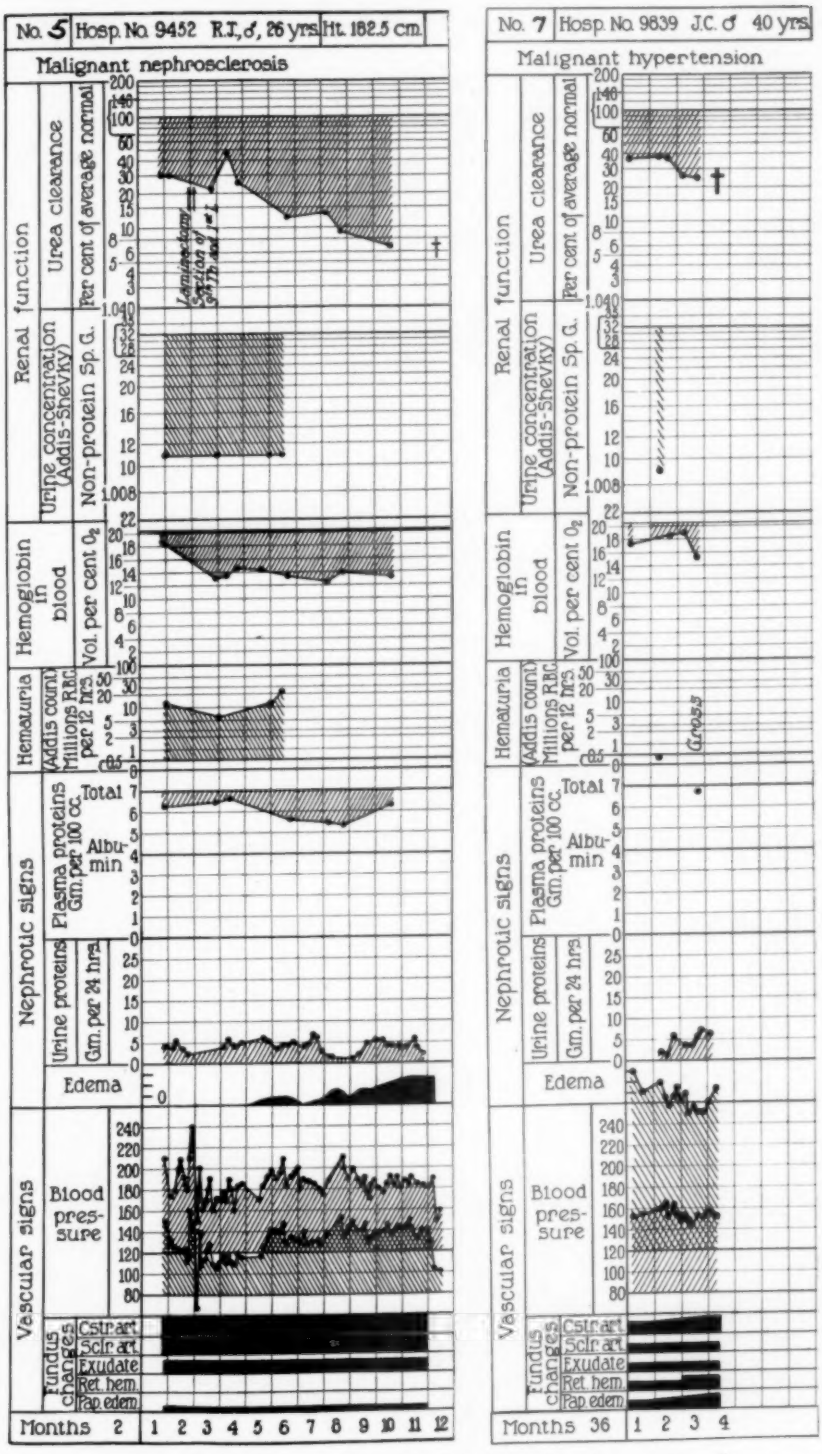

FIG. 4. Clinical and laboratory data depicting the course of malignant hypertension. Cases 5 and 7.

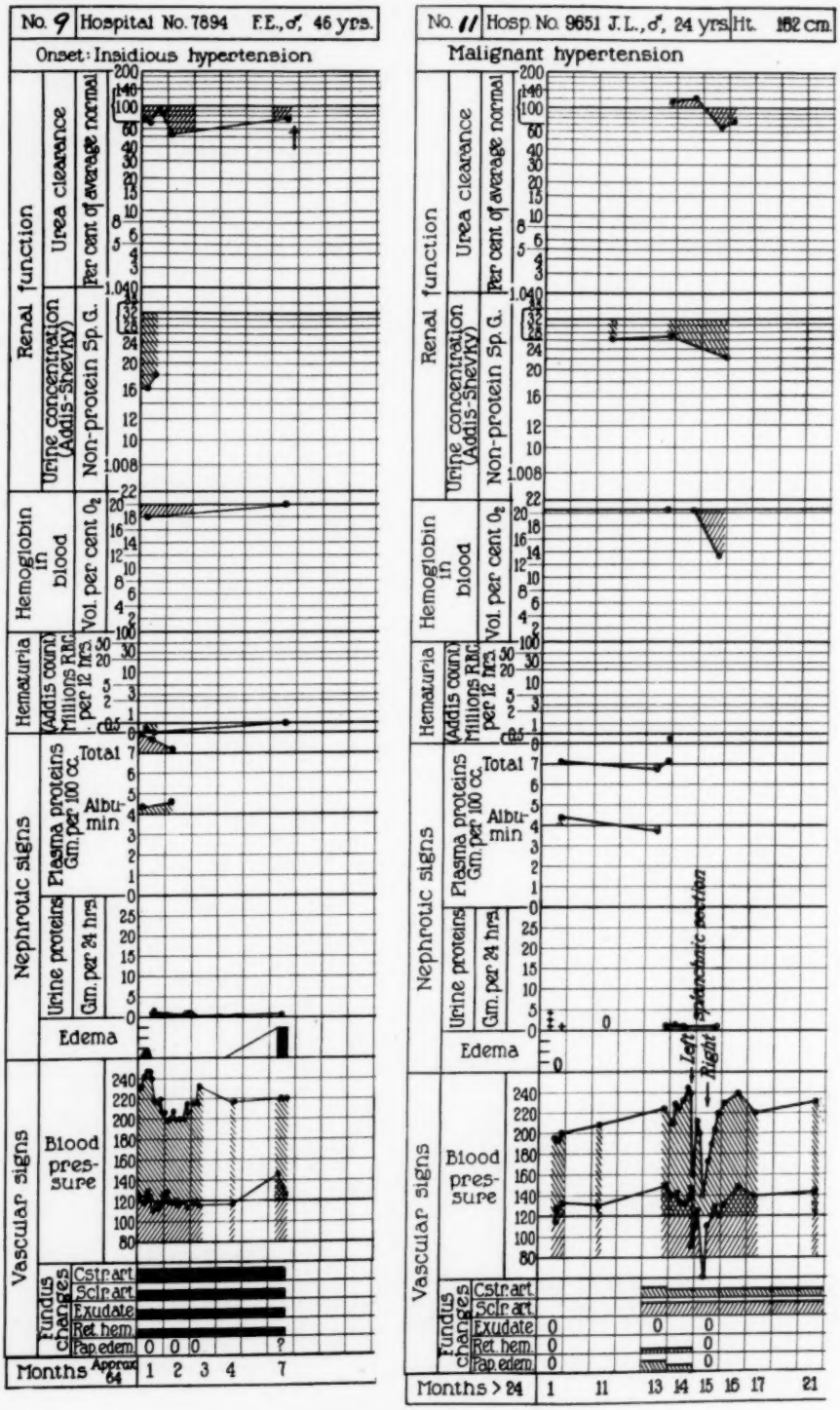

FIG. 5. Clinical and laboratory data depicting the course of malignant hypertension. Cases 9 and 11.

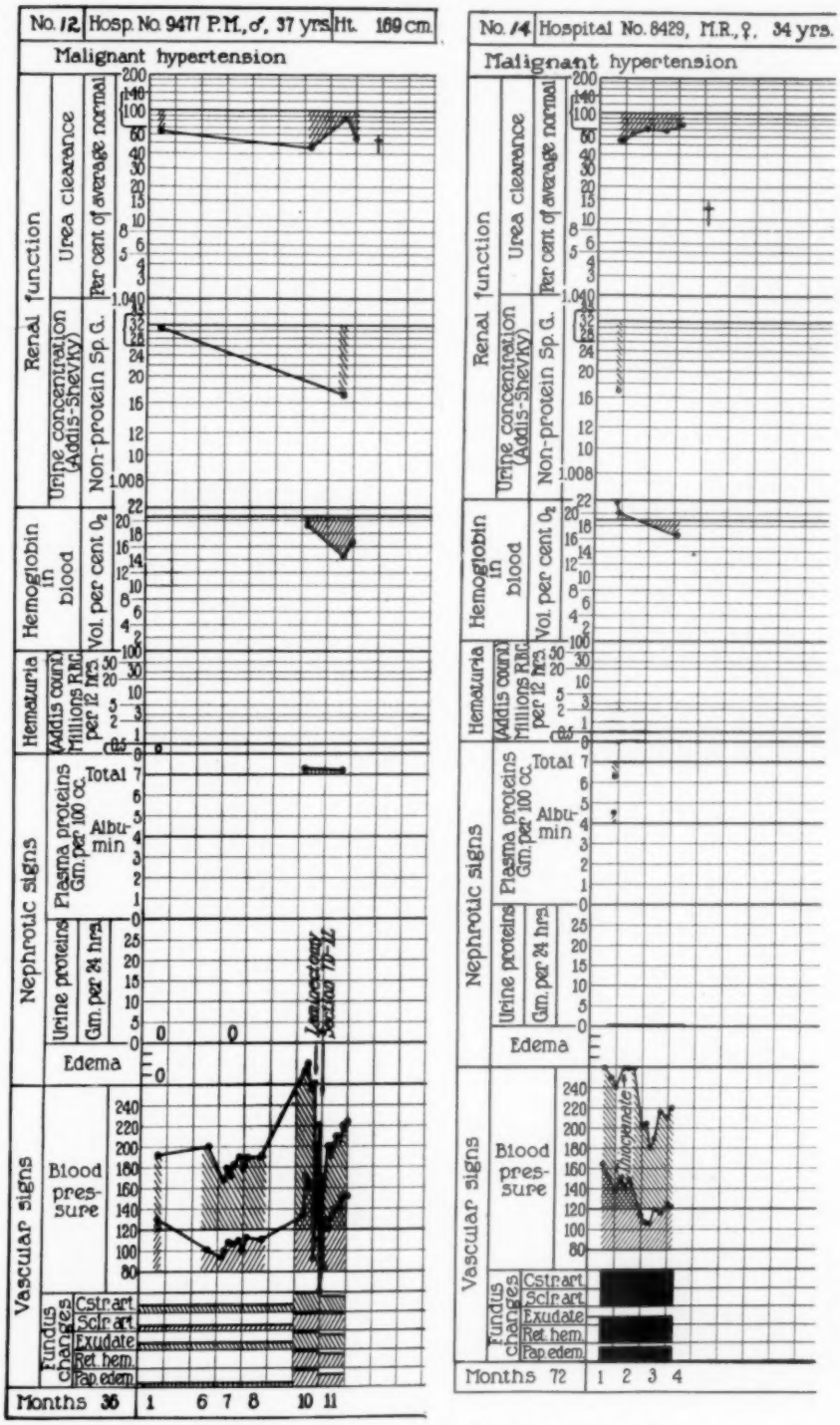

FIG. 6. Clinical and laboratory data depicting the course of malignant hypertension. Cases 12 and 14.

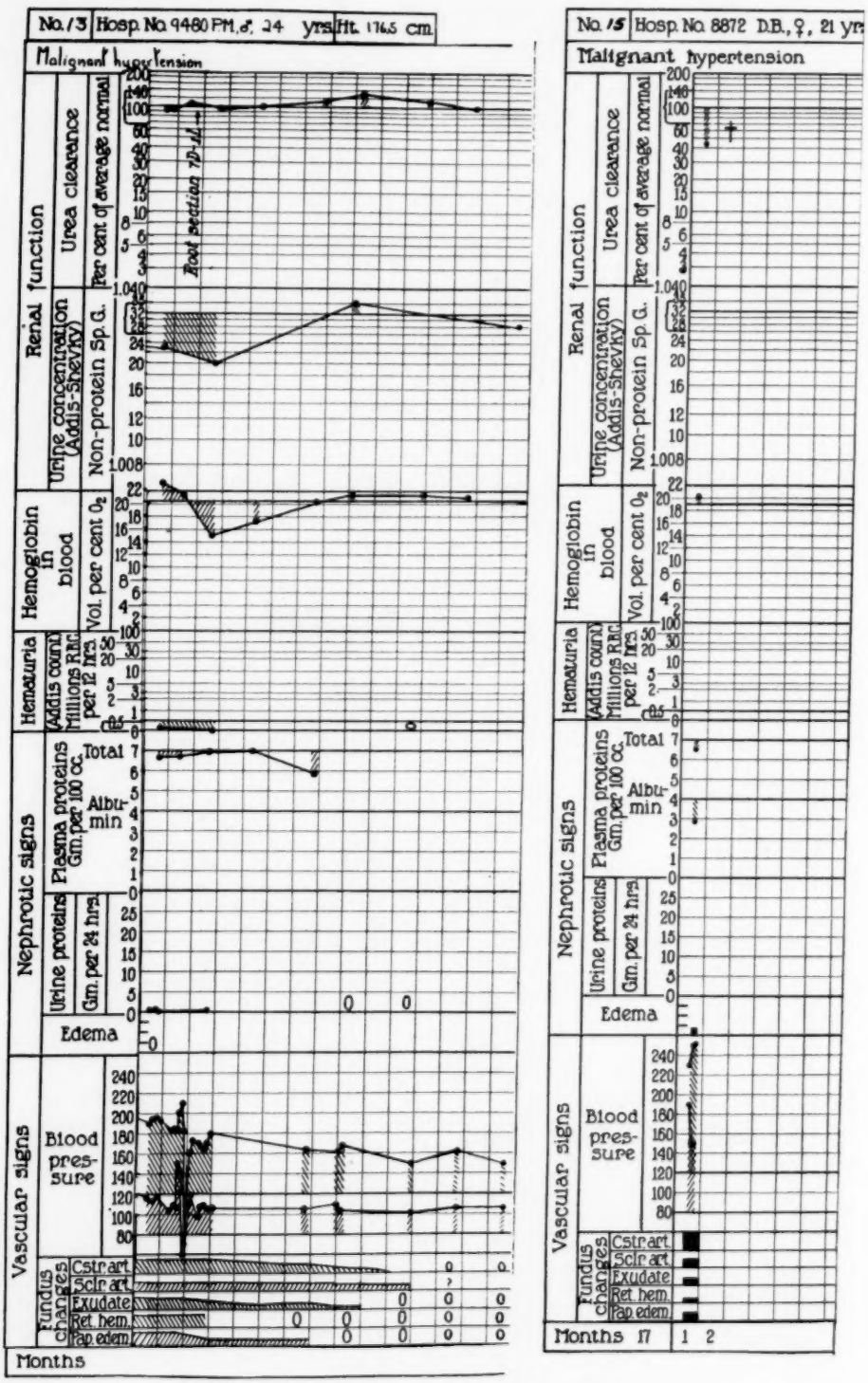

FIG. 7. Clinical and laboratory data depicting the course of malignant hypertension. Cases 13 and 15.

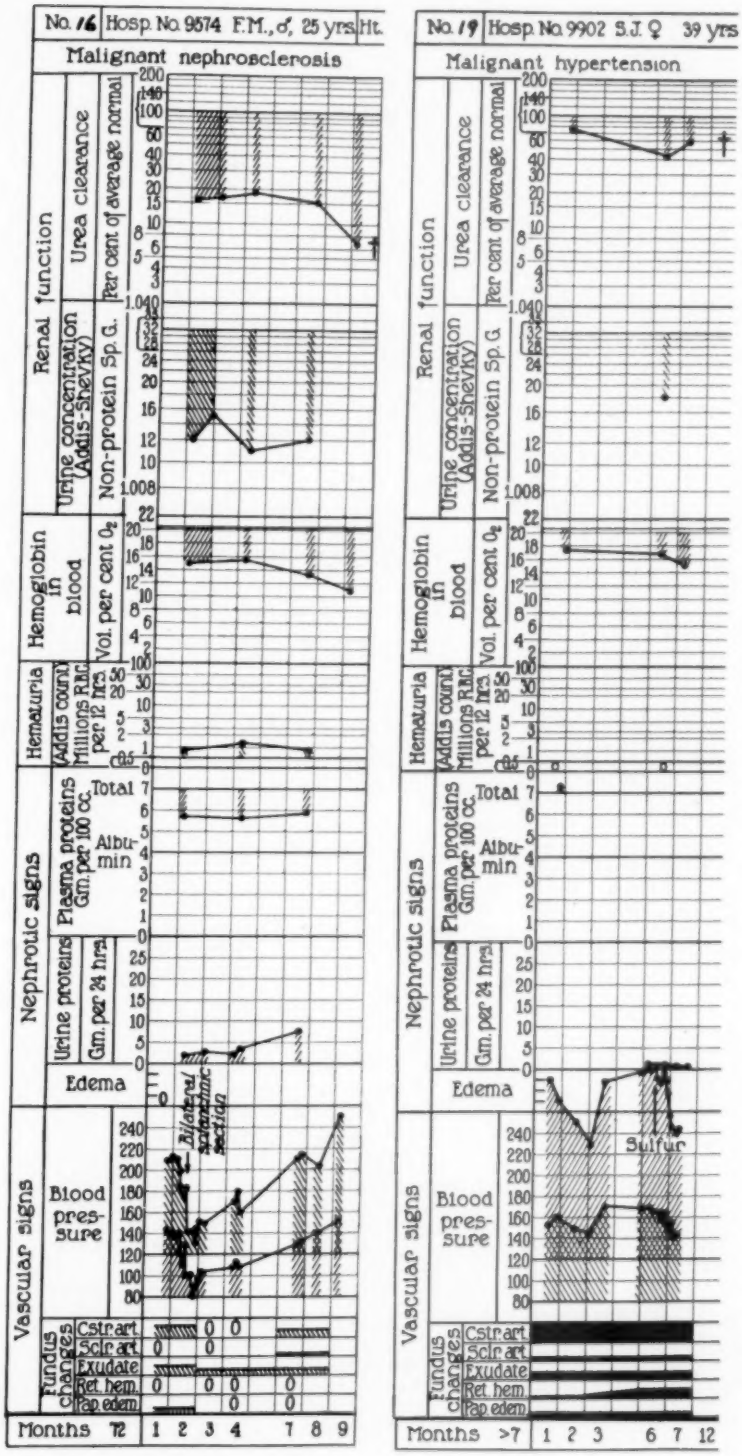

FIG. 8. Clinical and laboratory data depicting the course of malignant hypertension. Cases 16 and 19.

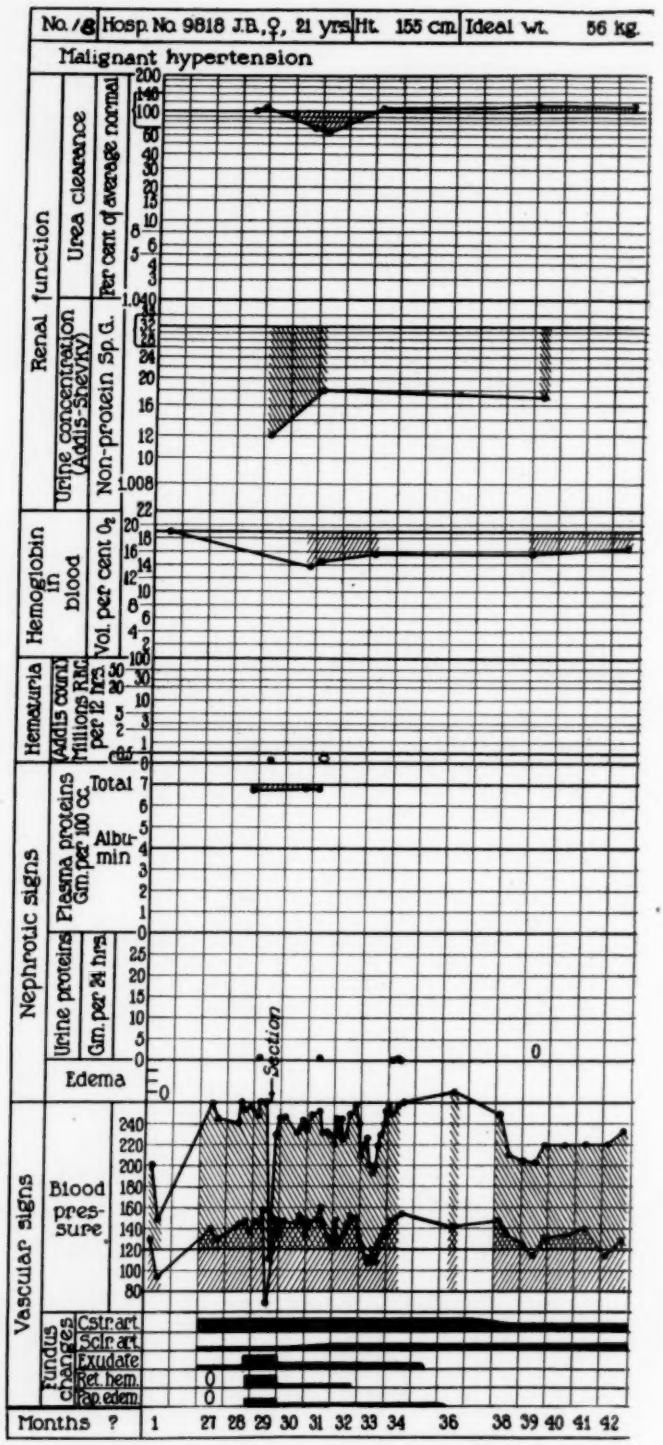

FIG. 9. Clinical and laboratory data depicting the course of malignant hypertension. Case 18.

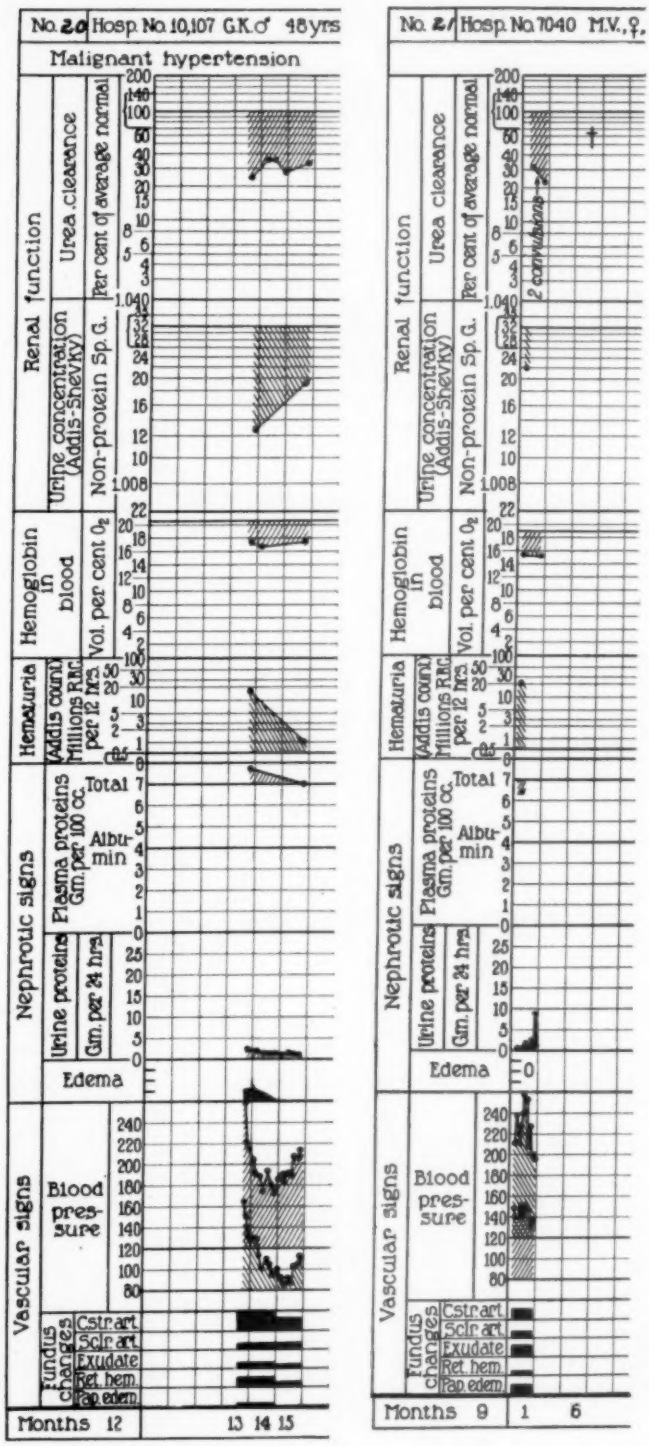

FIG. 10. Clinical and laboratory data depicting the course of malignant hypertension. Cases 20 and 21.

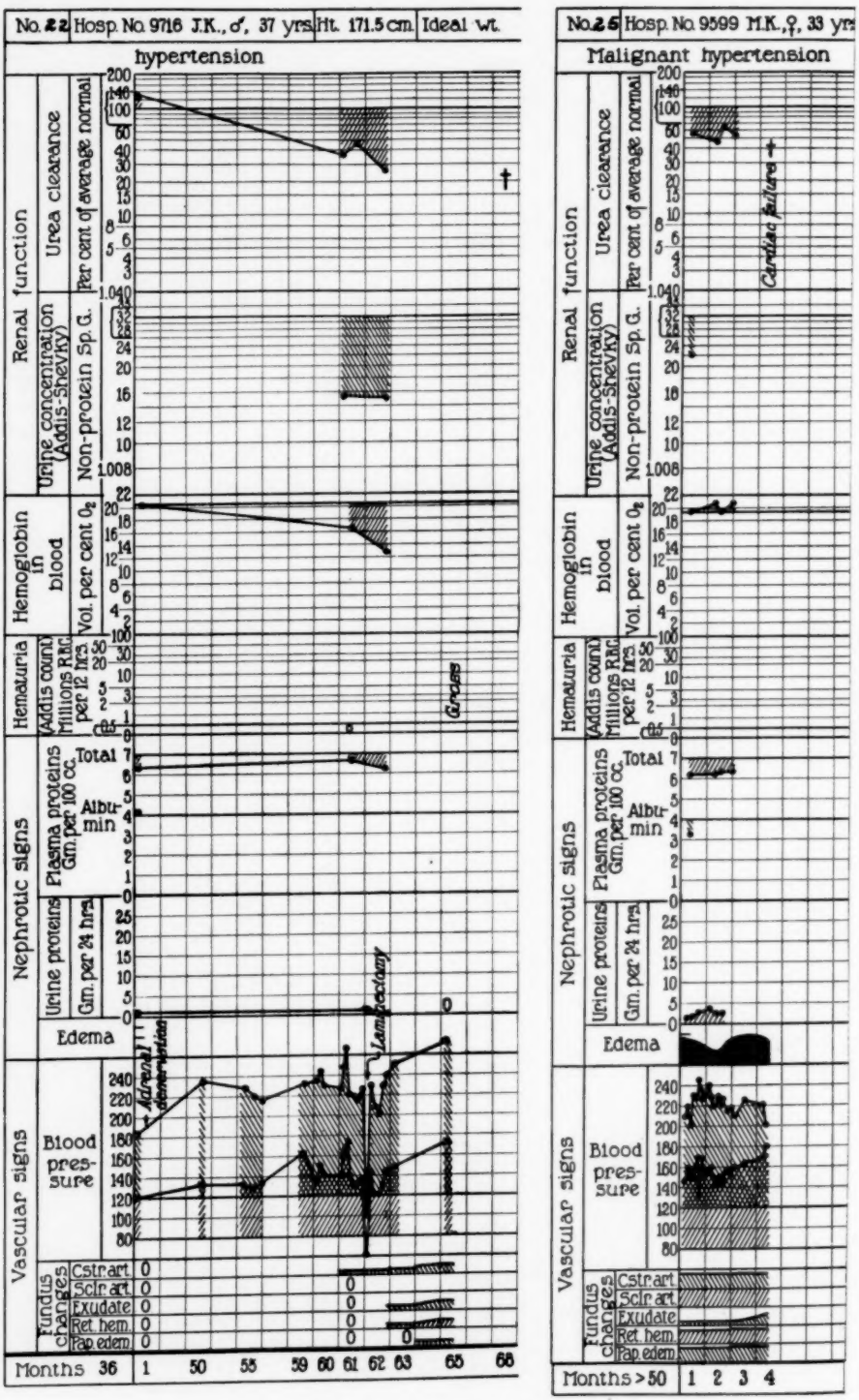

FIG. 11. Clinical and laboratory data depicting the course of malignant hypertension. Cases 22 and 25.

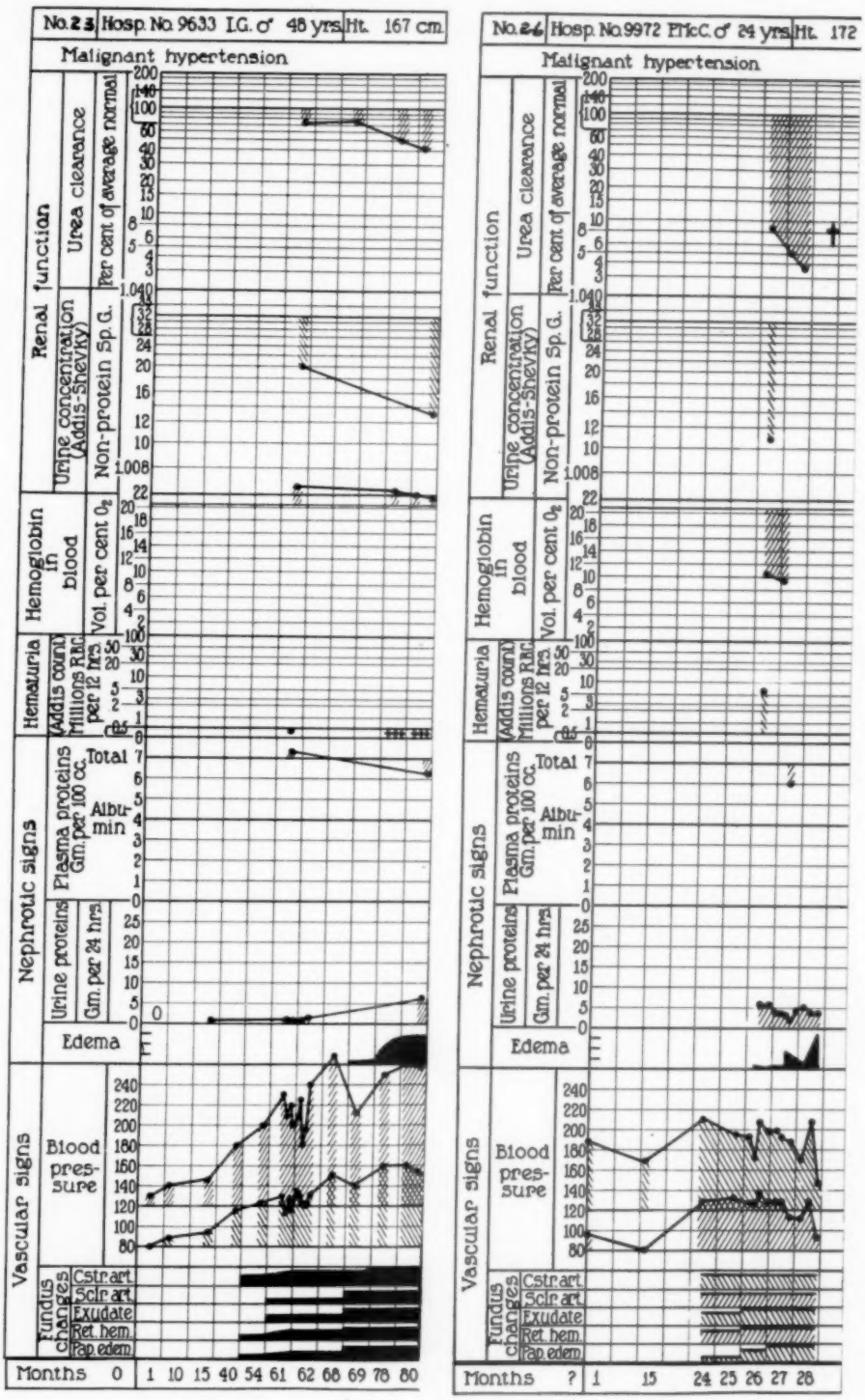

FIG. 12. Clinical and laboratory data depicting the course of malignant hypertension. Cases 23 and 26.

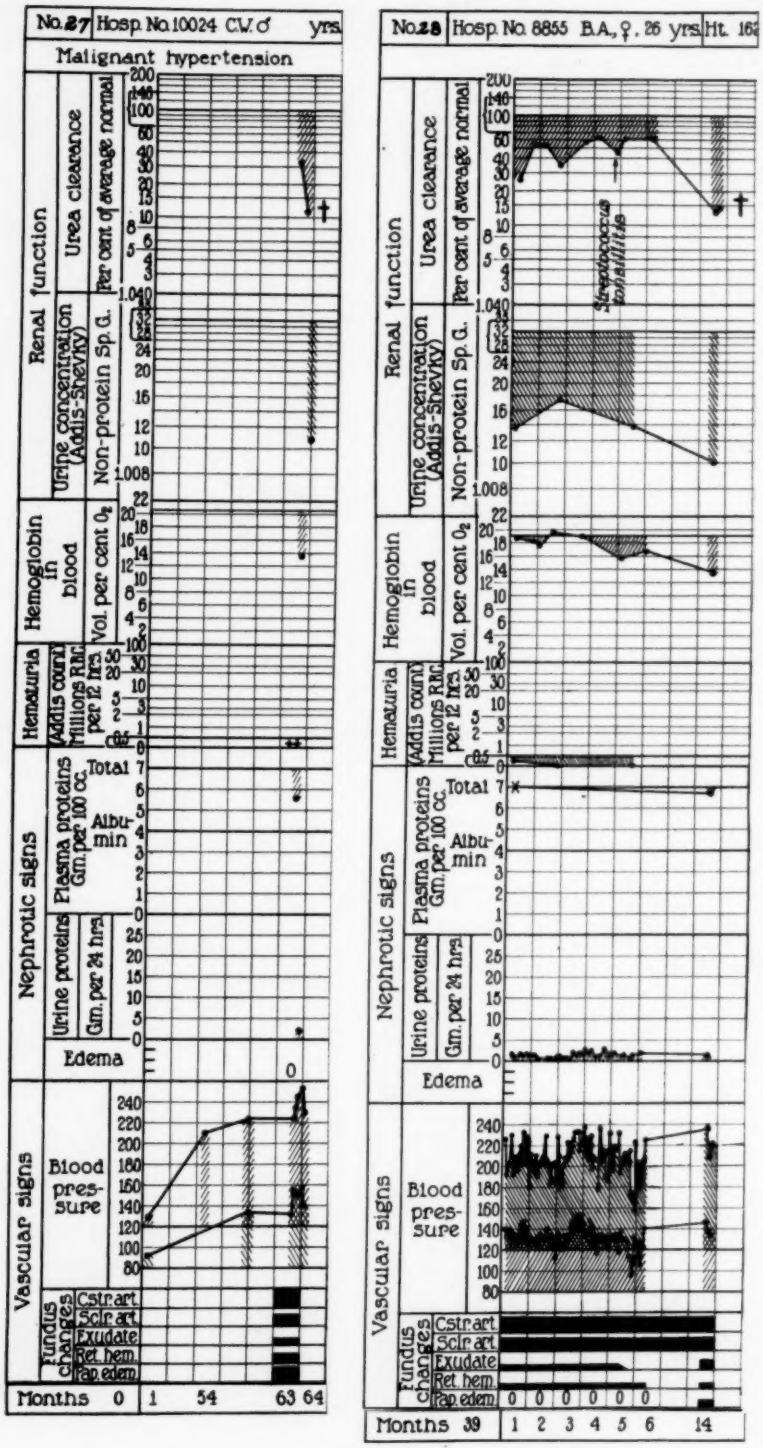

FIG. 13. Clinical and laboratory data depicting the course of malignant hypertension. Cases 27 and 28.

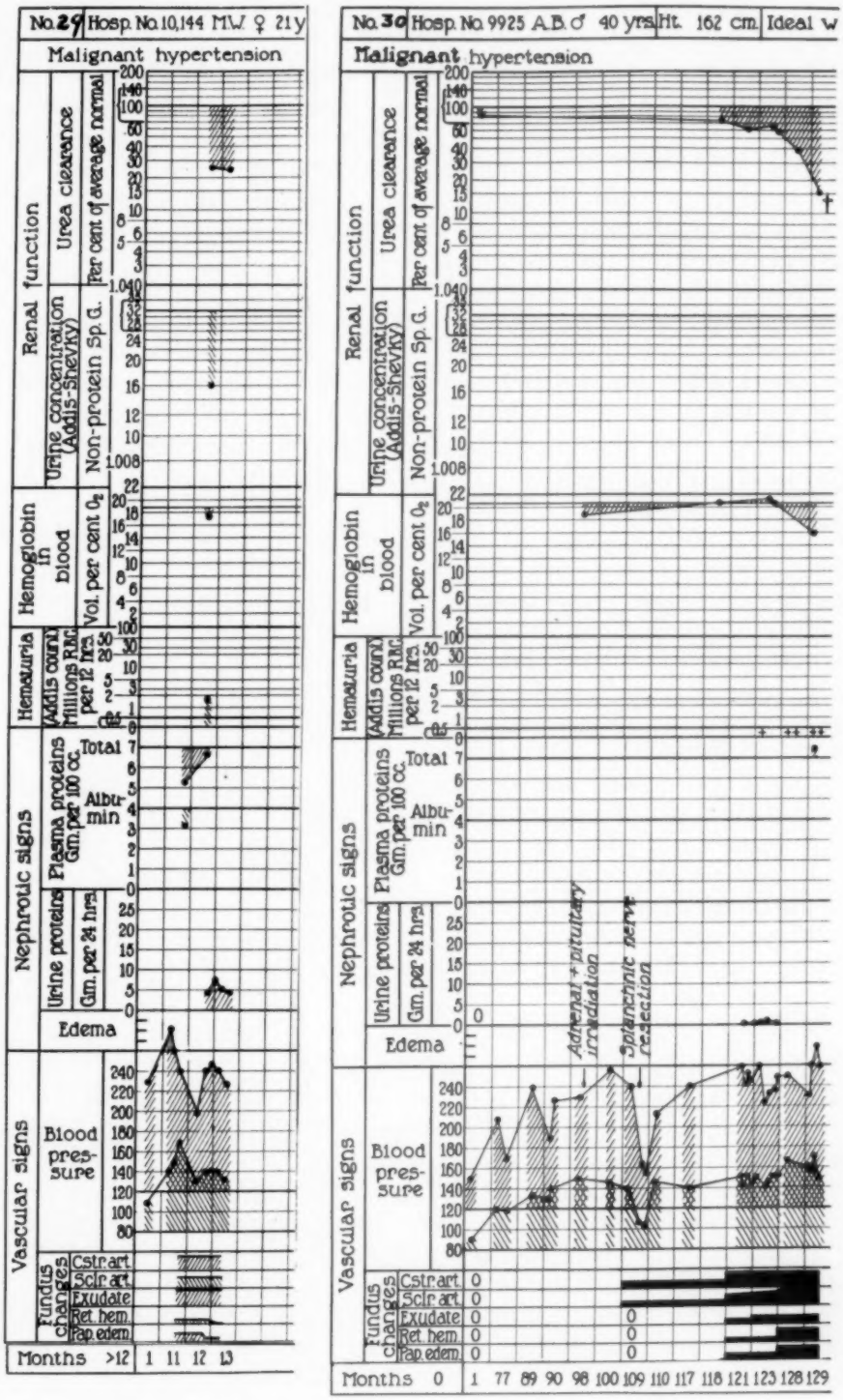

FIG. 14. Clinical and laboratory data depicting the course of malignant hypertension. Cases 29 and 30.

Discussion

The diagnosis of malignant hypertension was made in these 30 patients when the following morbid changes were observed: (1) hemorrhage and papilledema in the eyegrounds, (2) normal or moderately reduced renal efficiency (unless the disease was of relatively long duration), (3) rapid advance of the morbid changes (table 3), (4) elevated arterial pressure often with immoderately high diastolic pressure, (5) normal or slightly reduced plasma proteins and hemoglobin.

From the results of this study an attempt will be made to describe the usual course of malignant hypertension. It appears to be a syndrome of varied origin. Both male and female human beings suffer from it, males more commonly. It is a disease of early middle age, but may occur in youth or late middle age, seldom in old age. As a rule, hypertensive-vascular disease in the family is not common. It is not unusual for these patients to have had scarlet fever.

The chief complaints are headaches, visual disturbances, fatigue. These may occur singly or together. Far less frequent are dyspnea, convulsions, fainting, weakness, precordial discomfort, and edema of the ankles.

Signs and symptoms referable to special organs of the body may or may not be present. As a rule striking contrast exists between the neurotic behavior of patients with essential hypertension and equable emotions of those with malignant hypertension. Those archaic emotional patterns which the physician has learned to associate with essential hypertension occur but are not usual.

The heart, in particular the left ventricle, is responsible for dyspnea, which is common especially when the patients exercise. Pains referred to the heart and palpitations are frequent.

The kidneys produce few symptoms. Nocturia is usual, but ordinarily not troublesome.

Nausea and vomiting occur often. Weight loss of severe grade is also usual. Simultaneous occurrences of these symptoms and signs bode ill for the patient's life.

Impressive both to patient and physician is the sudden occurrence of blindness in one eye due to hemorrhage. Events such as this commonly inaugurate the syndrome and point to the ubiquity of the vascular involvement. That hemorrhage may occur within weeks or months after beginning rise in arterial pressure there is no doubt.

The results of physical examination usually convince one that the syndrome is rapidly progressive and bears little resemblance to the chronicity of essential hypertension. Papilledema, hemorrhage, exudate, intense arteriolar constriction, edema, detachment of the retina, and secondary glaucoma all speak eloquently for the aggressive qualities of this morbid process. The heart may not have time to hypertrophy, but dilatation of marked degree is not unusual.

TABLE III

Differential Diagnosis of Benign, Malignant Hypertension and Chronic Bright's Disease

	Benign Hypertension	Malignant Hypertension	Chronic Bright's Disease
Age	Usually above 20 years	Seldom below 9 years or above 55 years. Average 37 years	Any age
Onset	Insidious, often with nocturia	Rapid, often with retinal hemorrhage, dyspnea, headache	Either with acute nephritis or insidious with edema
Circumstances of onset	Often associated: emotional stress, Graves' disease, pregnancy, menopause	Usually none, but may follow several years after toxemia of pregnancy, essential hypertension, or scarlet fever	Often follows infections such as colds, scarlet fever, pneumonia. But association with infection often not demonstrable
Hereditary	Marked	Seldom	Seldom
Chief complaints	Headache, nervousness emotional instability, fatigue; there may be no complaints	Severe headache, dyspnea, blind spots	Edema, fatigue, dyspnea
Minor complaints	Blushing, lacrymation, perspiration, fears, choking sensation, palpitation, pressure over vertex, irregular menses, fleeting pains over heart, pounding in head, tinnitus, dizziness, irritability, pains in abdomen and limbs, dead fingers, temporary paralyses	Loss of weight, fatigability, nocturia, palpitations, temporary paralyses (hypertensive encephalopathy)	Nausea and vomiting, loss of appetite, nocturia, pain in back, pallor
Physical Examination	Well nourished, apprehensive, blushing, acne vulgaris often seen	Usually nothing noteworthy, but often orthopnea	Pale, often poorly nourished, skin may be doughy
Eyegrounds Disc	Normal	Hyperemic with edema	Normal except in advanced cases
Arterioles	Moderate constriction, often tortuous, slight arterio-venous compression, sclerosis	Intensely constricted, straightened, or tortuous, sclerosis	Normal or slightly constricted
Veins	Normal or tortuous and slightly dilated	Dilated and may be tortuous	Normal
Hemorrhages	Not found except in terminal phase	Usually present. Often appear and disappear rapidly	Only in uremia and often only in the last few days of life
Exudate	Rare	Always seen	Usually late in the disease

TABLE III—*Continued*

	Benign Hypertension	Malignant Hypertension	Chronic Bright's Disease
Edema of retina	Not seen	Common	Less extensive except late in the disease
Detachment	Rare	Often seen	Rare
Secondary glaucoma	Occasional	Occasional	Very rare
Thyroid	Often slightly diffusely enlarged	Seldom enlarged	Seldom enlarged
Lungs	Moist râles only terminally	Often scattered moist râles	Usually nothing
Heart	None to marked hypertrophy especially of left ventricle. Strong muscular beat with ringing A_2 and often P_2	Rapid enlargement. Gallop rhythm often present	Usually slow enlargement. Sounds of good quality or distant
Peripheral arteries	Often thickened	Rarely	Very rarely
Liver	Not enlarged except terminally	Often moderately enlarged and slightly tender	Rarely enlarged
Hands	Coarse tremor, sweating	Normal or slight cyanosis of nail beds	Normal
Laboratory Examination B. M. R. E. K. G.	Normal or moderately elevated. Left ventricular preponderance	Normal Left ventricular preponderance, inverted T-waves in Leads I and II	Normal Normal
Roentgen-ray of skull	Often thickening of anterior portion of skull	Pineal gland often calcified	Normal
Heart	Boot-shaped with moderate dilatation of aorta	Hypertrophy often more concentric with marked tortuosity and dilatation of aorta	Moderate hypertrophy
Spinal fluid pressure	Pressure normal or elevated if diastolic pressure very high	Usually very marked increase	Seldom
Blood pressure	Often labile Sys. 160 to 340 mm. Dias. 100 to 190 mm.	Seldom labile Sys. 200 to 260 mm. Dias. 130 to 190 mm.	Often labile Sys. 170 to 220 mm. Dias. 110 to 130 mm.
Urine-protein	3 grams/24 hrs.	6 grams/24 hrs.	6 grams/24 hrs.
Sp. gravity	Slightly reduced	Moderate or markedly reduced	Markedly reduced
Urea clearance	Normal	Moderately or sharply reduced	Usually reduced. In advanced cases below 1/5 normal

TABLE III—*Continued*

	Benign Hypertension	Malignant Hypertension	Chronic Bright's Disease
R. B. C. excreted	Normal numbers 500,000/12 hrs.	Often marked hematuria 1,000,000/12 hrs. or more	Usually hematuria 4,000,000/12 hrs. more or less
Casts	Small number of hyaline	Granular, blood and hyaline	Many casts of all types
Doubly refractile bodies	None	None	Occasional, especially in the nephrotic stage
Blood	Usually normal chemical constituents	Urea slightly elevated	Retention products such as urea, creatinine elevated in advanced cases
Hemoglobin	Normal or elevated	Moderately reduced	Often sharply reduced
Plasma proteins	Normal and elevated	Slightly reduced (5.5 to 7.0 grams/100 c.c.)	Often sharply reduced (below 5.0 grams/100 c.c.)
Lipemia	Not found	Slight	Often marked if the nephrotic stage is present
Course of disease	Slow, often extending 30 years or more	Usually fatal within 5 years	Usually fatal within 8 years
Termination usually by	Cardiac failure, apoplexy, uremia	Cardiac failure, uremia, apoplexy	Uremia, cardiac failure

Laboratory examination discloses that the heart is seriously injured. This is shown especially by inversion of the T-waves in Leads I and II. The function of the kidneys may be only moderately impaired until within weeks or months of death, at least as measured by urea clearance or the maximal ability to concentrate urine. The fact that more than the normal number of red blood cells is found in the urine indicates that the kidneys have not escaped morbid changes in their blood vessels.

Hemoglobin in the blood is normal or moderately diminished in the early stages. During the terminal phase it may be sharply reduced. These changes in hemoglobin resemble those of chronic nephritis rather than those of essential hypertension. While the syndrome of malignant hypertension is similar on the one hand to essential hypertension and on the other hand to chronic nephritis, enough differences usually occur to establish the diagnosis (table 3).

SUMMARY

The diagnosis and clinical course of 30 patients suffering from the syndrome of malignant hypertension has been described. Differential signs and symptoms elicited by both bedside and laboratory examination usually distinguish this syndrome from chronic nephritis and essential hypertension (table 3). It is emphasized that injury to the vascular system is widespread

and that the clinical picture is formed from the blending of manifestations of disorder especially in the heart, kidneys, eyes, and brain. The application and results of methods suitable for demonstrating and following the course of this syndrome are described.

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THE PROBLEM OF RHEUMATISM AND ARTHRITIS

REVIEW OF AMERICAN AND ENGLISH LITERATURE FOR 1937

(Fifth Rheumatism Review) *

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Part I

General Incidence of Rheumatic Disease; Social and Economic Importance. The United States Public Health Service, accomplishing a National Health Survey in 1935–36, made a house-to-house canvass of some 800,000 families comprising 2,800,000 persons in 83 cities and 23 rural areas in 19 States. The results of this survey, just published,[690] indicate that among chronic diseases in the United States *"Rheumatism" ranks first in*

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prevalence, second in producing disability, second in producing invalidity (permanent disability) and fourteenth in causing death. Among the 127,000,000 persons in the United States there are 6,850,000 with "rheumatism": thus there are almost twice as many cases of rheumatism as of its nearest rival, heart disease (3,700,000 cases), more than 7 times as much rheumatism as "cancer and other tumors" (930,000 cases), 10 times as much rheumatism as tuberculosis in all its forms (680,000 cases), and more than 10 times as much rheumatism as diabetes (660,000 cases).

Rheumatism was responsible for more days lost from work (97,200,000 days) than any other chronic disability except "nervous and mental diseases" (which caused a loss of 132,500,000 days of work). More days of work were lost because of rheumatism than from heart disease (95,200,000 days). Rheumatism produced more than twice as much disability as tuberculosis (41,400,000 days) and made more invalids (147,600 persons permanently disabled) than any other chronic disease except mental and nervous diseases (which produced 269,300 invalids). Rheumatism produced more invalids than did heart disease (144,200 invalids) and twice as many as all types of tuberculosis (77,900 invalids). Compared to its morbidity, the mortality rate of rheumatism is low—even so it was fourteenth on the list of chronic diseases and annually it causes about as many deaths (4400) as do goiter and other thyroid diseases (4700 deaths annually).

In this national survey "rheumatism included arthritis, gout, neuralgia, neuritis, lumbago, etc." One can hardly minimize the significance of these figures by suggesting that perhaps most of the cases were of hypertrophic osteo-arthritis in the elderly, because 50 per cent of the surveyed group were under 45 years, and 70 per cent were under 55 years, of age. Half of those permanently disabled were under 55 years of age. Indeed the real menace of rheumatism is probably not less, but much greater, than these figures indicate for when one realizes that about 40 per cent of all cases of "heart disease" result from rheumatic fever (McLean, 1933), to the toll of "rheumatism" in its broadest sense should be accredited many more hundreds of thousands of victims of rheumatic carditis (840,000 patients, according to Paul, 1930) with their millions of days lost from work.

The chairman of the committee to propose a national health program to the President of the United States recently reported to him that annually about 1,500,000 persons in the United States are disabled by "arthritis" and an additional 1,750,000 persons are annually disabled by neuralgia, neuritis and lumbago (Roche). Thus, by all accounts rheumatism is still the chief contender for the title "King of Human Misery."

Definition of "Rheumatism"; Content of "the Rheumatic Diseases"

But just what is rheumatism and what are the rheumatic diseases? As Woods said, the layman is likely to apply the term "rheumatism" to "a

wide variety of painful conditions from carcinoma of the stomach, through renal calculus, pleurisy, chronic osteomyelitis and vascular degeneration to the lightning pains of tabes." Thus to the layman rheumatism is more or less any ache or pain not inside the head or abdomen. In general, however, he applies the term to painful affections of the locomotor apparatus; that is, diseases of the joints, muscles, ligaments and bones. Thus, the real basis for his designation is not etiologic or pathologic, but anatomic. Vague as this concept is, that of physicians is hardly more concise. In the national survey, " rheumatism included arthritis, gout, neuralgia, neuritis, lumbago, etc." Many will object to this grouping. Thus Crowe insists that gout and those forms of arthritis due to a specific microbe are not rheumatic. But although he tells us what rheumatism is not, he too must share the charge of ambiguity for he defines " chronic rheumatic arthritis " as " all the residue of joint disease which is left after the exclusion of an injured joint and a specific arthritis." To him, then, atrophic and hypertrophic arthritis and chronic periarticular fibrositis would apparently all be rheumatic. But asks Woods: " Except that both are arbitrarily called rheumatic what similarity does fibrositis with its protean manifestations and even more protean complications bear, for example, to morbus coxae senilis? "

The fundamental point to determine is this: Is there any well defined pathologic lesion, environmental or immunologic reaction, or physicochemical abnormality the presence of which stamps one disease as rheumatic and the absence of which indicates that another disease is not rheumatic? Although the editors have carefully read over 3000 papers in preparation for these five Rheumatism Reviews [1-4] we have found no satisfactory answer to that question.

The word " rheumatism," derived from the Greek word " rheum " or humor, was first used in early Latin and Greek writings in a rather nonspecific sense to indicate the flow of a noxious humor from one affected region to another, not necessarily to joints. Thus, in those days one could really speak of " rheumatism of the stomach." Later the term was used more specifically to designate disease due to flow of a rheum or humor to joints. In this special sense Ballonius (1643) first used the word " rheumatism " to describe rheumatic fever. Later the term was applied to other skeletal affections including painful conditions of muscles and fibrous tissues supposedly due to a discharge floating in the body. From time to time pathologists tried to describe some basic tissue lesion of rheumatism, a common denominator between the rheumatic diseases, which was supposedly a rather characteristic inflammatory reaction in fibrous tissue, especially in heart, skeletal muscles and joints, but this distinction has not been upheld by time. The nodular fibrous lesions in rheumatic fever, atrophic arthritis and fibrositis, although somewhat alike, are not indisputably identical; certainly they are absent in many conditions which physicians persist in calling rheumatic. Therefore Woods called the terms " rheumatism," " rheumatoid " and " rheumatic diseases " etymological nonsense.

If then there is as yet no accepted basic pathologic or physicochemical reaction pathognomonic of the rheumatic diseases, why do we persist in using such an unscientific term? Its continued use is not merely due to tradition;

it has survived because of its practicality. It is a handy label for a group of diseases which has acquired no better or shorter designation. By common understanding, the kernel of this disease-group consists of rheumatic fever, atrophic arthritis, myositis and fibrositis. But although this kernel can be fairly well defined, like an ameba with a shifting periphery, the term " rheumatism " has engulfed some foreign matter, diseases such as gout and " gonorrheal rheumatism," which have nothing in common with the kernel except that they involve the same structures, the locomotor apparatus, producing therein symptoms which at times may resemble those of " true rheumatism." In the last analysis, then, the concept of the physician largely resembles that of the layman. In reality physicians generally use the term " rheumatic diseases " in the same broad anatomic sense as do their patients.

The editors of these Reviews have always used the term " rheumatism " in a broad sense, preferring to foster a wide outlook on the problem. The " rheumatism service " of a hospital may be dedicated chiefly to the care of, let us say, patients with rheumatic fever, chronic arthritis and muscular rheumatism. But all too often the rheumatism service is the refuge for the patient whose skeletal aches and pains are really due to unsuspected hyperparathyroidism, or whose " sciatica " arises from a cord tumor, or ruptured intervertebral disk, or whose " rheumatic hip " represents a metastatic bone malignancy or multiple myeloma, or perhaps for the patient with the painful, stiff hands of scleroderma or with the sore muscles of dermatomyositis. Therefore it has seemed proper to discuss herein many conditions which admittedly have no remote etiologic connection with each other but are somewhat related in an anatomic sense. Hence, under the designation " diseases of joints and related structures," which for our purpose is more correct than the term " the rheumatic diseases," will again be included a review of whatever information would seem to be helpful to the physician whose patient is going to confront him, saying, " Doctor, I think I have rheumatism."

Classifications of Diseases of Joints and Related Structures

The year 1937 was unique: practically no new classifications of rheumatic diseases were proposed! Aware of the difficulties involved, writers this year successfully repressed the almost irresistible urge to erect new classifications. A few writers offered sound criticism of existing classifications. The only real basis for an accurate classification and nomenclature is an etiologic one but so far this has been only partly possible. The next best classification would be one based on a study of morbid anatomy but even here knowledge is inadequate. Classification then must be largely clinical, supported by radiography. Fortunately such classifications are very useful but into them, whenever possible, should be introduced terminology based on such knowledge of etiology as we have (Woods). Warren, Hinton and Bauer have done this in their classification of joint diseases, as follows:

A. Joint diseases of known etiology

1. Traumatic; e.g., associated with internal derangement, fractures into joints, etc.
2. Infection; e.g., due to the gonococcus, tubercle bacillus, streptococcus and other organisms.
3. Neuropathic; e.g., associated with tabes, syringomyelia, leprosy.
4. Metabolic; e.g., associated with gout.
5. Constitutional; e.g., associated with hemophilia.
6. Anaphylactic; e.g., associated with serum sickness.

B. Joint diseases of unknown etiology

1. Degenerative joint disease (degenerative, hypertrophic or osteo-arthritis).
2. Rheumatoid arthritis (proliferative, atrophic or chronic infectious arthritis).
   - (*a*) Typical.
   - (*b*) Atypical (often called "nonspecific infectious arthritis" because the causative bacteriologic agent cannot be demonstrated).
   - (*c*) Spondylitis deformans, Strümpell-Marie or von Bechterew type, or rheumatoid arthritis of the spine.
3. Rheumatic fever.

[Since the causes of gout and hemophilia are unknown, some might object to the inclusion of gouty and hemophilic arthritis under the heading "joint diseases of known etiology." The distinction between typical and atypical rheumatoid arthritis will be discussed later under "atrophic arthritis."—Ed.]

According to Poynton, he who would separate the rheumatic diseases sharply is likely to be embarrassed by finding "border-line cases"; he who would link them all together, assuming a common diathesis, will be embarrassed to find that the classical examples of the various forms appear so different from one another that they must surely be entirely different in nature and causation.

Diseases of Joints Related to Trauma

In view of the frequency with which persons seek compensation for alleged traumatic arthritis, physicians should be familiar with accepted criteria for distinguishing true primary traumatic arthritis from non-traumatic arthritis affecting a joint subjected to subsequent trauma. In previous Reviews the criteria of others have been given. Those of Morrow are: (1) The trauma of a specific accident must be severe enough to produce acute inflammation (synovitis) of the affected joint—pain, swelling, effusion, dysfunction. (2) The traumatized joint must be the only one showing such inflammation. (3) It should be established that prior to the alleged injury articular function was normal, but the patient's statement to that effect does not constitute proof thereof. (4) Progressive articular changes may occur and in time be demonstrable clinically and roentgenographically; these changes should appear within a "reasonable limit of time," sometimes within six weeks, generally within three to six months. Any changes delayed 18 months or more after an accident can hardly be attributed to the accident. When posttraumatic intra-articular osseous changes do occur they are us-

ually hypertrophic in character, resembling those of ordinary senescent (degenerative, hypertrophic) osteo-arthritis.

Forms of chronic recreational, occupational or postural microtrauma which produce articular lesions were discussed by Bernstein and Fisher. To such trauma knees seem especially vulnerable. Although external, internal and crucial ligaments are powerful stabilizers of the knee joint they are inadequate to keep knees stable in every position; the support of surrounding muscles is even more important. Years after an acute articular injury the end results of old trauma may be hypertrophic villous synovitis and osteoarthritis, with degeneration of cartilage and hypertrophy of marginal bone.

Athletic injuries most frequently affect knees; the common results therein were reviewed by Tucker. Direct violence to the knee may produce synovitis, contusion of the quadriceps muscles or their expansions with or without synovitis, prepatellar bursitis or bruising of the infrapatellar fat pad, or fracture of the patella or fibular head. Common results of indirect violence were synovitis from violent flexion or rotation of the knee, injury to lateral ligaments from lateral wrenches, and damage to the anterior cruciate ligament, infrapatellar fat and alar folds, posterior capsule or popliteus tendon after violent extension. The diagnosis of these different lesions was discussed.

Ochsner defined a simple, uncomplicated sprain as an injury to any or all of the articular components without fracture, rupture of a tendon, fragmentation of cartilage or persisting dislocation. The severity of pain, degree of discomfort and duration of incapacity from sprains vary greatly depending on such factors as the extent of the sprain, patient's age, obesity and muscle tone but especially on the treatment used. Unless treated promptly and efficiently an acute sprain may become chronic and persistently or intermittently painful for years. Permanent articular weakening with muscle atrophy may ensue, even limitation of motion or recurrent synovitis.[21, 502]

To study the pathologic histology of sprains, Miltner, Hu and Fang produced experimental sprain of varying severity in knee joints of rabbits. One week after mild sprains there developed articular swelling, synovitis (edematous membrane, focal hemorrhages, slight pannus, hydrops), edema, capillary congestion and cellular infiltration in subsynovial tissues, capsule and ligaments. Tissues were grossly normal in four weeks but microscopic evidence of inflammation persisted two weeks longer, ending in complete healing. [This suggests that sprained joints should be protected for at least two weeks after clinical signs have disappeared.—Ed.] A similar but more severe reaction was produced by more severe sprains. Injury to ligamentous insertions and fibrillar degeneration of surface layers of cartilage were seen. The inner, free portion of the semilunar cartilage on the traumatized side showed slight necrotic changes; after six weeks the distal free ends showed more advanced fibrillation with exfoliation of superficial cells and hyalinization of deeper cells. At the eighth and tenth weeks some specimens showed

complete degeneration of the free portion of semilunar cartilages. Cartilage heals slowly and incompletely; in certain cases the inflammation may become chronic and cartilage degeneration may predispose to changes in the more vascular articular structures with the full development of chronic traumatic arthritis.

Laboratory Data. Certain laboratory procedures help to confirm the diagnosis of acute traumatic arthritis. If anemia, leukocytosis, abnormal Arneth count and increased erythrocyte sedimentation rate are present, the condition is probably not traumatic arthritis. More valuable data can be obtained by analysis of synovial fluid. According to Collins the total polymorphonuclear leukocyte count of synovial fluid in acute traumatic arthritis is always less than 1000 cells, generally less than 500 cells, per cu. mm., whereas in atrophic arthritis it is always over 1000, generally over 5000 cells, per cu. mm. In acute traumatic arthritis the icteric index of synovial fluid is over 5 because of bilirubin from hemorrhage; in most inflammatory effusions it is below 5 (Kling). [Some cases of traumatic arthritis with hemorrhage into joints have an icterus index below 5.—Ed.]

The intra-articular injection of CO_2, air or other gas, or of some contrast medium such as abrodil, permits roentgenographic visualization of the soft parts within joints; this was considered valuable in the diagnosis of traumatic arthritis as it often promptly revealed lesions not otherwise visible, such as tears in the cartilage, hypertrophy of synovial membrane, narrowing or obliteration of the suprapatellar or infrapatellar spaces or posterior compartment of the knee due to adhesions or proliferation of tissue (Bernstein and Fisher; Kling).

Treatment. Much "chronic industrial rheumatism" is produced by delay in treatment or by inadequate treatment of traumatized joints in the earliest stages. It is most important to treat the earliest lesion by suitable rest, physical therapy, and the subsequent protection of the vulnerable joint from repeated injury (Collins). Significant effusions should be promptly removed by aspiration; this provides considerable relief and permits cytologic and chemical studies of the fluid so helpful in differential diagnosis. Kling and Sashin again recommended histamine ionization. Injured knees were treated by Tucker by variable amounts of rest, bandages and casts in the more severe cases, heat and massage, aspiration of effusions, faradic contractions, manipulative movements and above all special care to avoid undue wasting of the quadriceps muscle.

Tucker prescribes a schedule of graduated remedial exercises for affected knees. The first exercises avoid weight bearing: (1) twitching and contracting the quadriceps muscles for two minutes every hour while lying on a couch; (2) with knees bent and legs dangling over the edge of a couch, alternate extension and flexion of each knee, 20 such complete movements twice daily, increasing by 5 movements each time; (3) raising the extended leg by flexing the hip while lying flat; abducting the thigh at the hip, then adducting it; (4) bicycling as the patient improves; (5) as synovitis disappears weight-bearing exercises are prescribed: while holding the back of a chair, heel raising, knee bending and straightening; (6) skipping.

Bernstein and Fisher performed arthrotomy to remove hypertrophied synovial membranes, loose bodies and bony spurs.

The best treatment for simple sprains is proper strapping with adhesive; this provides adequate support and rest; Ochsner considered it " universally successful " but said, " few medical men seem to know how most effectively to apply the straps." Therefore Ochsner diagrammed the technic of applying straps to the commonly affected sites—ankle, wrist, knee, sacro-iliacs. He added a practical point regarding the removal of adhesive. Rather than using gasoline, kerosene, ether or other inflammable or explosive chemicals, the attendant should put about 1 teaspoonful of cold cream into the palm of one hand, rub the hands together for a moment and then rub the cold cream well into the adhesive plaster bandage which can then be removed with a minimum of discomfort.

The rôle of trauma in the pathogenesis of atrophic, hypertrophic and tuberculous arthritis, of diseases of the intervertebral disks, and of muscle affections will be discussed hereinafter in the sections devoted to these diseases.

Gonorrheal Arthritis and Gonorrheal " Rheumatism "

Incidence. Gonorrhea is much more prevalent than any other serious communicable disease. In the United States there are annually 1,037,000 cases of acute gonorrhea. In addition, similar number of patients seek treatment for chronic gonorrhea. There are constantly under observation and treatment 493,000 persons with gonorrhea in this country, and the disease is apparently not on the decline. A fourth of the patients are females; approximately 230,000 potential American mothers acquire the disease in each year. Such are the estimates of Vonderlehr and Usilton of the United States Public Health Service, based on its 1935 survey. Older statistics indicate that the joints of from 1 to 5 per cent of gonorrheal patients become infected. Thomas regards the lower figure as more accurate since gentler, less traumatizing treatment of urethritis became the vogue. Only one of Wishengrad's 251 male adults developed gonorrheal arthritis. Only three of Wilson's 76 adult female patients developed joint pains; none had true arthritis. However, two (7 per cent) of Drummond's 28 adults had " joint involvement." According to Benson and Steer who summarized the combined statistics of others, arthritis occurred in 15 (2.6 per cent) of 565 cases of gonorrheal vaginitis in children. But no arthritis developed among 68 girls with lower genital tract infection treated by Reichert, Epstein, Jung and Colwell.

Why do some patients develop, others escape, articular complications? According to Pelouze, metastatic complications such as arthritis are preponderantly the result of trauma to the urogenital focus: " One has but to survey the treatment accorded patients or to study the patient's doings prior to the onset of arthritis to demonstrate the truth of this statement." Thus Keefer and Spink [365] noted articular exacerbations after vigorous prostatic

massage. Another writer [660] suggested a different hypothesis: In persons of the "acid type" (who eat too little calcium-containing food and prefer acid condiments and those foods which yield an acid residue) gonorrheal urethritis "is associated with further toxic effects which cause a constitutional disturbance such as allows of the development of a coincident protozoon and it is this which is responsible for the gonorrheal arthritis."

[This statement is given without proof of any sort.—Ed.]

Clinical Data: Criteria of Diagnosis. Criteria for a diagnosis of proved gonorrheal arthritis, as used by Keefer and Spink,[365] were: (1) a history of recent gonorrhea; (2) evidence of genital gonorrhea; (3) a positive gonococcus complement fixation test on blood or on synovial fluid or both; (4) a demonstration of gonococci in synovial fluid. The criteria of Warren, Hinton and Bauer for "proved gonorrheal arthritis" were: (1) a history or physical evidence of previous or existing gonorrhea, (2) a history of joint disease consistent with recognized characteristics of gonorrheal arthritis, (3) the isolation on smear or culture of gonococci from the primary focus or synovial fluid. "Probable gonorrheal arthritis" can be diagnosed when the first two criteria are present but the third absent.

[These criteria are exact as research demands, but these authors noted cases in which, because of the absence of some of the usual clinical features, diagnosis was particularly difficult until the eventual discovery of gonococci in joints, blood stream or both. Whenever possible these criteria should be used in general practice but when bacteriologic or serologic tests are negative or unavailable, yet the patient presents a genital infection, or recent history thereof, and acute arthritis of the type hereinafter described, a presumptive diagnosis is justified, certainly to the extent that a therapeutic test should be instituted at once; a prompt response greatly strengthens the presumption.—Ed.]

Symptoms and Course. In an excellent survey of 140 proved cases of gonorrheal arthritis Keefer and Spink described its features. Although described in previous Reviews we shall summarize them briefly because, with the advent of the new highly successful methods of treatment, early recognition of gonorrheal arthritis is especially important.

Generally within 10 to 20 days (but occasionally much later [645]) after the onset of genital (less frequently conjunctival or rectal) gonorrhea, acute arthritis appears, often abruptly, and more often polyarticular than monarticular. Fever and leukocytosis (generally moderate) and an elevated erythrocyte sedimentation rate are usually present. Curiously a respiratory infection often precedes the arthritis; in connection with febrile polyarthritis this often leads to an erroneous diagnosis of rheumatic fever. Articular and periarticular inflammation are generally intense. Any joints may be affected, most often knees, ankles and wrists. These joints are often involved in an intense tenosynovitis without definite arthritis. Juxta-articular muscles may waste rapidly without histologic evidence of acute inflammation therein. Since acute tenosynovitis occurs more often with gonorrheal than with any other type of arthritis, its presence should arouse suspicions of gonorrhea. First polyarticular and often migratory, the arthritis may soon become stubbornly monarticular. The acute process lasts from a short time to several weeks or longer. The commonest "complication" (which occurred in 15 per cent of the 140 cases) is conjunc-

tivitis which may appear with the arthritis or appear and disappear before the arthritis; the conjunctival exudate reveals no gonococci.

Of the 140 patients of Keefer and Spink, 104 were in males, 36 females; 107 of the cases were polyarticular, 33 monarticular. The following joints were affected (numbers refer to cases): knees 127, ankles 56, wrists 44, fingers 31, metacarpophalangeal 27, metatarsophalangeal 27, shoulders 25, hips 23, elbows 20, toes 19, lumbar spine 14, sacro-iliacs 8, heels 7, cervical spine 6, dorsal spine 4, sternoclavicular 3, temporomandibular 3, costosternal 2, acromioclavicular 1, olecranon bursa 1. Tenosynovitis affected ankles in 32 cases, wrists in 19, metacarpophalangeal in 6, metatarsophalangeal in 6, knees in 4 and fingers in 4 cases. Abscess of a tendon sheath occurred twice. Iridocyclitis, a serious complication which may impair vision, occurred in 4 cases. Death occurred in 7 of the 140 cases, three times from intercurrent pneumonia, twice from endocarditis, once from glomerulonephritis and once from "progressive gonococcic infection."

Unusual Features and Complications. Several reports described unusual complications of gonorrheal arthritis. A young female patient of Sloane and Sloane developed gonorrheal arthritis of a knee and hip. Acute intrapelvic protrusion of the femoral head into the acetabulum (Otto pelvis) developed and progressed in spite of treatment by traction and splints. Bacteremia *without* endocarditis was present in three cases of Keefer and Spink. It was associated with a striking cutaneous eruption, maculopapular, in some areas hemorrhagic, rapidly becoming vesicular, then pustular. It was most intense over extremities and was never seen without bacteremia. Hazel and Snow noted a case of gonococcic septicemia without endocarditis but with arthritis and a generalized purpura with the petechiae more marked on palms and soles. Reviewing the literature Gillespie and Thompson concluded that culturally proved cases of gonorrheal endocarditis are rare; they reported three such cases (two with arthritis) with cultural and necropsy data, an incidence of 0.15 per cent of 1947 cases of gonorrhea. Petechiae were present in skin, pericardium and pleura. A patient of Cromer with gonococcal endocarditis (clinical diagnosis) slowly recovered after several transfusions. Williams noted two such patients; one died, the other rapidly recovered after two sessions of fever therapy. The patients of Cromer and of Williams exhibited petechiae described as "small red sore spots" or slightly tender, circumscribed, purplish red areas, 2 mm. to 1 cm. in diameter, chiefly on extremities; many showed a central white area of necrosis; a few showed vesiculation with seropurulent fluid. Two of Keefer and Spink's [365] patients developed gonococcic endocarditis and died. Only nine cases of gonococcal aortitis have been reported; Nichol and Dobrin described a case of gonorrheal arthritis with acute gonococcal aortitis and aortic endocarditis, multilocular aortic aneurysm and a congenitally bicuspid aortic valve.

Keratodermia blennorrhagicum affected four of Keefer and Spink's cases of gonorrheal arthritis. Acute hemorrhagic glomerulonephritis may accompany gonorrheal endocarditis. It is rarely seen without endocarditis but Keefer and Spink noted it in two cases of gonorrheal arthritis without endocarditis; one patient died, cultures of the kidney were sterile.

The diagnostic significance of the more common "complications" was emphasized by Keefer and Spink. Conjunctivitis may accompany post-dysenteric arthritis, rarely rheumatic fever, but most commonly gonorrheal arthritis. Hence, acute arthritis with conjunctivitis or with keratodermia suggests gonorrhea. Acute polyarthritis with tenosynovitis, a history of gonorrhea, conjunctivitis or iridocyclitis and a cutaneous eruption should always suggest that the arthritis is gonococcal.

Pathology. No new data on articular pathology were presented. Keefer and Spink summarized the studies of Keefer, Parker and Myers [2] (1934).

Roentgenograms. No new studies were reported.

Laboratory Data. "Smear-method." The inspection of smears of genital or other exudates properly stained by Gram's method has many merits; it is simple and inexpensive; the report can be obtained in a few minutes; smears on glass slides are easily transportable. They are unreliable when stained with methylene blue. The smear method is much less dependable in chronic cases, when few gonococci and many secondary invaders are present. Unfortunately there is no uniformity in making or staining smears in our public health laboratories. Such were the conclusions of Carpenter who, as a Committee Referee, reported to the American Public Health Association the Committee's approved methods of obtaining, examining and interpreting smears and cultures.

2. Cultures. The cultural method of McLeod and his associates (1934) is "the most reliable available procedure for diagnosing gonococcic infection." The technic was redescribed.[100, 101]

3. Gonococcal complement fixation test. Some regard this test as unreliable; others consider it sufficiently reliable for routine use. Warren, Hinton and Bauer performed 614 tests on serums from 316 patients with various types of arthritis and concluded that it was an important diagnostic aid. Of 125 tests in 74 cases of proved or probable gonorrheal arthritis 82 per cent gave positive reactions at some time during the arthritis; only 18 per cent were negative. Consistently positive reactions on every test were found in 81 per cent of 52 "proved cases" and in 64 per cent of the probable cases of gonorrheal arthritis. Of 239 cases of nongonorrheal arthritis, 92 per cent gave consistently negative reactions. The test was also approved by Cohn, who made 1153 tests on 495 patients with proved or suspected gonorrhea (only seven with arthritis). Keefer and Spink found positive reactions in blood in 85 per cent of 83 cases of gonorrheal arthritis, and in synovial fluid in 66 per cent of cases. Tests on synovial fluid were never positive unless those on blood were positive; the latter were more reliable and more frequently positive.

In interpreting the test the following must be remembered.[127, 701] The production of complement fixing antibodies is dependent on the duration and spread of the infection. In acute, uncomplicated cases of gonorrhea localized to the superficial urethral or cervical mucosa, the test may be negative as insufficient antibodies are

absorbed. In acute complicated cases, such as cases of arthritis, the test is generally strongly positive. The test is not as specific as the Wassermann reaction and is far more delicate. The present technic is not sufficiently accurate for one to rely on any one test or even on repeated tests in a given case; tests should be interpreted only in association with clinical and bacteriologic features. Some cases of proved or probable gonorrheal arthritis and some of nongonorrheal arthritis give intermittently positive and negative tests. There is a 10 per cent chance that any positive test is falsely positive. Since a negative test occurs in about 20 per cent of gonorrheal cases, a negative reaction does not entirely rule out gonorrhea. The test may be negative even in proved cases of gonorrhea because it may have been done prior to the appearance of antibodies (it generally takes 10 days to 4 weeks, occasionally 5 to 24 weeks, after the initial infection for enough antibodies to accumulate in the blood to give a positive test) or because it may have been done after the disappearance of antibodies. Some patients in the last stages of infection lose the power of producing them. A test may be negative because of imperfections in the method or because the antigen employed may not have been prepared from enough different strains and may not contain the strain infecting a particular patient. According to Tulloch (1922) there are five chief antigenic strains of gonococci; 72 per cent of all cases are produced by one main strain. In the past the antigens used have not had a sufficiently wide range of activity. Warren, Hinton and Bauer used 4 strains; Cohn used 12 strains.

Comparative value of smears, cultures and complement fixation tests. Of 92 patients with a history and symptoms of gonorrhea Carpenter obtained positive smears in 38 per cent, positive cultures in 50 per cent, and positive complement fixation tests in 87 per cent. Nevertheless he considered complement fixation tests unreliable because false positive reactions were obtained in 71 per cent of 28 patients without evidence of gonorrhea by history, symptoms, examination, cultures and smears. [This percentage of false positives is much higher than that obtained by others.—Ed.] Furthermore, extremely variable results were obtained on sera of the same four patients when sent to eight different laboratories. Carpenter admitted, however, the test was likely to be much more reliable and valuable in cases of metastatic infection, such as arthritis.

4. Synovial cytology, chemistry. One hundred fourteen samples of synovial fluid from 83 patients with gonorrheal arthritis were examined (Keefer and Spink [365]). In 26 per cent of 78 cases the fluid was culturally positive; in 74 per cent the fluid was sterile. The total cell count per cu. mm. was 7000 to 236,000 in the former; 1600 to 120,000 in the latter. The total protein content was that of an exudate in both types (3.5 to 6.0 gm. per 100 c.c.). The nonprotein nitrogen was the same as in blood. Infected synovial fluid contained less sugar, sterile fluids contained the same amount of sugar as blood.

5. Bactericidal tests of blood and synovial fluid. Spink and Keefer [363, 643, 644] noted that during a gonococcic infection bactericidal antibodies against the homologous infecting strain appear in the circulating blood. Their interpretation follows. They probably represent the patient's defensive response to his infection and are largely responsible for localizing and killing the infection. They increase during the course of gonorrhea or gonorrheal arthritis. When enough specific antibodies have developed to kill the infecting organisms, articular repair proceeds. Gonococci are killed in vitro by lysis produced by sensitization of bacteria by antibody. Then destruction is completed by complement. Phagocytosis of bacteria is not an important feature. Serum agglutinins do not develop and agglutination tests are of no value in diagnosis or in studying the immunity mechanism in gonorrhea. The bacteriolytic antibodies diffuse from blood into synovial fluid. In sterile joint fluids the antibacterial antibodies are present in amounts equal to or slightly less than in blood; but in patients with infected joint fluid the fluid contains no bactericidal anti-

bodies and that of whole blood is low or only moderately elevated. When gonococcemia is present no bactericidal antibodies are found but when the bacteremia ceases antibodies appear in blood. Thus the prevention of bacteremia seems to depend on the antibody content of blood or on an efficient local defense reaction in the primary focus of infection.

Keefer and Spink noted that gonococci localize and survive in areas amply supplied with mucin; e.g., in urethra, cervix, conjunctiva and joints. Perhaps mucin is a favorable medium for gonococci or somehow helps them survive. It was found that synovial mucin assists some strains of gonococci to survive, especially when synovial fluid antibodies are low. But when the antibody content of synovial fluid is high, synovial mucin does not prevent the bactericidal action of the fluid. Synovial fluid also contains antitryptic substances which probably protect cartilage from destruction by the tryptic-like ferments of leukocytes.

Diagnostic Value of Laboratory Tests. In cases of typical gonorrheal arthritis diagnosis is relatively easy. In other cases diagnosis may be difficult because the arthritis may appear long after an initial genital infection or because the disease may mimic other arthritides.

Case reports were given illustrating these difficulties and the usefulness of laboratory tests therein (Warren, Hinton and Bauer; Spink and Keefer [645]): cases of acute polyarthritis, later proved to be gonorrheal, in women unaware of latent, persistently asymptomatic genital infection; cases of proved gonorrheal arthritis in men who had not had acute genital gonorrhea within 18 months to 5 years and in whom during arthritis no genital gonorrhea could be found; cases of gonorrheal arthritis preceded by respiratory infection in patients, unaware of genital infection —hence simulating rheumatic fever; cases in which proved acute gonorrheal arthritis developed during pregnancy in women with or without discoverable genital gonorrhea.

In such cases the combination of close clinical observation and laboratory aids is necessary. Sometimes preliminary laboratory tests may be misleading but a suspicious clinical picture will force one to continue the eventually successful search for positive laboratory data. In other cases the clinical picture may be misunderstood and a complement fixation test, done routinely in difficult cases, may provide the first clue to the true nature of the disease. In other words the starting point for an accurate diagnosis must be a healthy suspicion of the presence of gonorrhea, which initiates the proper correlation of clinical and laboratory observations. An aid to the development of the proper suspicion is the realization that "the gonorrhea patient is perhaps the most inveterate liar in the realm of medicine." [733]

It would appear, however, that the matter of suspicion can be considerably overdone, for one physician [108] wrote: "It is my belief that gonococci are responsible for considerable of the muscle and joint pains in patients over forty. For the past ten years patients over 40 complaining of vague aches and pains of muscles or joints have been routinely given mixed gonorrheal vaccine. The results have been just about 99 per cent perfect—with either complete cessation of symptoms or marked improvement. . . . Cases of osteo-arthritis, myalgia, tenosynovitis report an increase of symptoms the day following injection and then steady improvement. I give this treatment regardless of venereal history."

[This is carrying suspicion to the *n*th degree!—Ed.]

Treatment of Gonorrheal Arthritis

The past six years have seen the development of the two greatest advances ever made in the treatment of gonorrhea and gonorrheal arthritis: the use of fever therapy (1932 et seq.) and more recently the use of sulfanilamide.

Fever Therapy for Gonorrheal Arthritis. During 1937 about 15 reports presented the results of fever therapy in about 380 cases of gonorrheal arthritis. Bierman, Horowitz and Levenson reported further experiences with their "combined heating technic." Systemic fever (106.5° F. for 12 to 14 hours) was accomplished by short wave diathermy; during six to eight hours of this fever the pelvic temperature was increased to 108 to 110° F. by the use of pelvic diathermy electrodes. Especially for women does this technic provide a superior method of curing genital as well as articular infections.[53] One report[51] noted results in 31 cases of gonorrheal arthritis: there was "complete restoration of joint function" in 26 cases (84 per cent); no improvement in 3 cases in 2 of which bony ankylosis required arthroplasty; 2 patients were lost sight of. A later report[54] summarized their total results (overlapping series 1935-1937): In 80 per cent of 40 cases of acute or chronic gonorrheal arthritis, previously treated unsuccessfully by other methods, "joint symptoms subsided with remarkable uniformity immediately after the termination of (an average of three) treatments."

Seventeen patients with gonorrheal arthritis (duration unstated) were treated by Potter, Redewill and Longley. From 5 to 10 weekly sessions of fever (8 hours at 103 to 105° F.) were given: "all cases showed rapid improvement and remarkable cures" even those in which the disease had lasted a year or more. [In our experience gonorrheal arthritis rarely remains active this long; in such cases the diagnosis should be reconsidered.—Ed.] It was believed that the intravenous injection of "mercurochrome 1 per cent in glucose 50 per cent" aided patients to respond to hyperpyrexia. Doses were given on three alternate days during six days prior to the sessions of fever. [No control studies were reported and no evidence was given to substantiate this opinion.—Ed.]

Forty patients with gonorrheal arthritis (duration unstated) were given two to four sessions of fever, each of six hours at 106 to 107° F., by Newman and Berris: 30 (75 per cent) of these patients were "completely cured"; marked improvement was noted in 4 cases with bone destruction but short wave diathermy and massage for two months were required to restore good function. Thomas treated 53 patients: of 48 who had acute conditions, 46 (95 per cent) were promptly "symptomatically cured"; 5 patients with "chronic gonorrheal arthritis" were "markedly relieved." Purcell's two patients with acute gonorrheal arthritis were also "completely relieved."

Of 23 patients with gonorrheal arthritis (duration unstated) treated by Simmons with fever therapy 15 (66 per cent) were promptly "cured" (complete cessation of pain and inflammation but not necessarily complete return

of normal function). After fever gonococci were found in urethral smears in only 2 of these 15 cases. There was "marked relief" in 4 cases (17 per cent), little or no relief in the remaining 4 cases (17 per cent), probably because of inadequate fever. It was concluded that a minimum of 25 hours of fever (106 to 107° F.) is necessary to cure most cases.

[Some believe that this amount of heat is often not required.—Ed.]

Two girls, aged 13 and 3 years, with acute gonorrheal vaginitis and arthritis were markedly improved by 1 and 2 sessions of fever respectively, given by Spekter and McBryde. Forty-three patients were treated by Gwynn: arthritis had been present for 1 week to 5 years; in 24 cases it was acute (8 weeks or less). Results were not summarized in the usual manner but "the average improvement of the entire group was 90.2 per cent." Most of them had been unrelieved by other treatments prior to fever therapy; all but one had "negative" urethral smears after fever therapy. Simpson and Kendall have now treated 47 patients with acute and 28 patients with chronic (8 + weeks) gonorrheal arthritis: "All evidence of active arthritis was abolished in all cases." In 67 cases (89 per cent) all evidence of genitourinary infection disappeared during treatments (three to five sessions of fever, each five to seven hours at 106 to 107° F.). All of four patients treated by Cheetham and Roemer were cured after one to six sessions of fever.

[To obtain a normally functioning joint the disease must be cured before permanent damage takes place; unfortunately the latter may occur within two to three weeks.—Ed.]

Pettit favored the use of short (three to four hours) sessions of fever (105 to 107° F.) induced by hot water baths for the treatment of genital gonorrhea, especially of pregnant women, but his results in gonorrheal arthritis were not good: of four patients treated one was cured, one markedly improved; two (50 per cent) were not improved.

[Apparently amounts of fever were inadequate.—Ed.]

Schnabel and Fetter reported their further experiences: of 49 patients with acute gonorrheal arthritis (less than six weeks' duration) 37 (76 per cent) were "cured," 7 (14 per cent) were markedly improved, 5 (10 per cent) moderately improved. The average period of hospitalization for the 49 patients was 22 days after fever therapy was begun. Of 21 chronic cases, in which the average duration of symptoms was 6.3 months, in 5 cases (24 per cent) the patients were cured, in 8 (38 per cent) markedly, and in 8 (38 per cent) moderately, improved. The average period of hospitalization in these 21 chronic cases was 35 days after fever therapy was begun. To prove that fever therapy was a superior method, an equal number of patients treated by other means than fever was studied. Of 49 patients with acute conditions treated *not by fever* but by physiotherapy to joints and local chemotherapy to genital lesions, only 4 (8 per cent) were cured

(compared to 37 cases or 76 per cent of the fever-treated group) and 45 improved. Of 21 patients with chronic conditions *not* treated by fever therapy, only 1 (5 per cent) was cured (compared to 5 cases or 24 per cent of the fever-treated group); 19 were improved and one died. The average period of hospitalization in cases in which fever was not used was just twice as long in the acute cases (45 days) and 3½ times as long in the chronic cases (156 days) as it was in those in which fever was used.

[This report deserves special commendation as it is the first one in which such a comparison has been made.—Ed.]

In five cases acute gonorrheal arthritis was promptly cured by Solomon and Kopp. Brodribb treated four patients with acute gonorrheal arthritis or fibrositis " with great success "; all obtained immediate relief from pain.

[The latter report includes a comprehensive review of fever therapy, its methods, indications and results, and is notable because it apparently represents the first British report on results in gonorrheal and nongonorrheal arthritis.—Ed.]

A patient with acute gonorrheal tenosynovitis of a foot was successfully treated by incision and drainage of pus and by two applications of radiotherapy (Reeves).

Summary. The results given in these 15 reports agree with those noted in previous Reviews [3, 4]; indeed they are somewhat better, as might be expected with further experience and the use of higher temperatures for longer periods. Thus, about 90 per cent of these 380 (circa) patients with acute or chronic gonorrheal arthritis were " cured," made symptom-free. Fever therapy was regarded as a " specific," [551] " the procedure of choice," [279] " the best treatment now available," [619] " the treatment of choice to be used at the earliest available opportunity " [54] in gonorrheal arthritis. In such cases " the proper application of fever therapy should be the first thought." [673] Results were of course better in acute than in chronic cases where irreparable articular damage had often already occurred. In some cases poor results were obviously due to inadequate amounts of fever. In general, sessions of fever consisted of five to six hours at 106 to 107° F. (rectal). Usually three or four, occasionally only one or two, sessions of fever were required, given at intervals of three to five days. Since a certain percentage of patients continue to give " positive urethral smears," even after joints have been cured by fever, the " combined method " of general and local heating described by Bierman and his colleagues, seemed especially indicated in cases of resistant local infection.

Fever Therapy for Nonarticular Gonorrhea

The beneficial effects of fever therapy on gonorrhea without arthritis were given in a number of reports. Most patients were promptly cured.[20, 497, 543, 555, 641, 723]

Thus, 93 per cent of 121 women with gonorrhea treated by Bierman and Horwitz became " gonococcus-free " after an average of two treatments. Results in

172 cases of Potter, Redewill and Longley were generally excellent except in cases of chronic posterior urethritis. Of 189 patients of Desjardins, Popp and Stuhler, 90 per cent were "cured"; 10 per cent were improved in varying degrees. Results were better when sessions of fever were given closer together, every third day, and were longer, at first five or six hours, later eight, ten or twelve hours. In 90 per cent of the cases, from one to five treatments were needed, in 10 per cent from five to ten sessions were required to eradicate gonococci. All evidences of gonorrhea were abolished by fever therapy alone in 92 per cent of Simpson and Kendall's 38 cases, given an average of four sessions of fever, five to seven hours each.

Of particular interest was the report of Parsons, Bowman and Plummer: 43 patients were given fever therapy; 44 others were treated by older methods. Eleven in each group had "acute gonorrhea": 73 per cent of each group were cured but it took only 27 days (av.) in the first group, 81 days (av.) in the others. Fourteen in each group had acute prostatitis with complications: 86 per cent of those given fever were cured in an average of 22 days; 71 per cent of those treated otherwise were cured in an average of 84 days. The remaining 37 patients had chronic prostatitis with complications: 89 per cent of 18 given fever were cured in an average of 28 days; only 32 per cent of the 19 treated otherwise were cured and it took an average of 105 days.

However, only 6 of the 10 patients of Cheetham and Roemer were cured of urethritis after an average of 4 sessions of fever, 5 to 6 hours at 105.5 to 106° F. Because of similar failures to cure gonococcic infections by a single or by repeated short sessions of fever, Warren, Scott and Carpenter used one session of fever at 106.7° F. (41.5° C.), long enough to kill each patient's particular strain of gonococcus (av. 14.8 hours); of 31 patients so treated, 81 per cent were cured. The procedure was not devoid of risk; one patient died. Because estimations of the thermal death time of each patient's gonococcus are difficult and generally impracticable, Simpson and Kendall advocated one 10 hour session of fever; preliminary results indicated that most patients will respond favorably to such single sessions. "One-treatment cures" were also obtained by Bierman and Levenson who applied "combined heating" for 12 to 14 hours.

[Although single sessions of fever of more than 10 hours' duration may be successful they increase materially the responsibilities of the physician and the risk to the patient. It now seems likely that the use of sulfanilamide, alone or combined with short sessions of fever, may obviate the necessity of long sessions.—Ed.]

Fever Therapy for Gonococcemia and Gonorrheal Endocarditis

Warren [702] reported one case in which gonorrheal septicemia was cured by prolonged fever therapy. Hazel and Snow also cured a patient with gonococcic septicemia, purpura and arthritis by two sessions of fever, each of 5 hours, at 105.6 to 107.8° F. A patient with gonococcal arthritis, severe sepsis and probable gonococcal endocarditis (but with negative blood cultures) recovered promptly after three sessions of fever given by Williams. In another case of Williams, results were unsuccessful: a patient with proved gonococcal endocarditis and arthritis died of syphilitic cirrhosis of the liver and uremia although the blood was sterilized from the fever. Repeated sessions of fever, given to a patient with gonococcemia, seen by Krusen and Elkins, temporarily sterilized the blood but the patient died of endocarditis and nephritis.

General Remarks on Fever Therapy

Historical aspects of the development of fever therapy and notes on the various means of producing artificial fever were reviewed by several.[51, 75, 334, 525, 544, 564, 586, 614, 622, 638, 641]

Physicians indicated their *preferences for different methods* of producing fever: by the Kettering hypertherm,[279, 600, 619, 622, 673] General Electric Fever Cabinet,[111] Kimble Cabinet,[551, 564] diathermy,[613] electromagnetic induction,[25, 597] air-conditioned cabinets with electromagnetic induction,[498] preheated cabinets,[497] radiant energy cabinets,[641] humidified heated cabinets,[555] inductothermy,[25, 614] hot water bath,[543, 578] short wave therapy,[288, 336, 384, 737] vapothermy,[506] "blanket-method."[217] Evidence required by the Council on Physical Therapy of the American Medical Association for consideration of apparatus used in fever therapy was stated.[162]

[The choice of apparatus, provided it is safe and easily controllable, is of little concern; most important is the careful supervision of patients during treatment.—Ed.]

The physiologic effects of fever therapy as given in previous Reviews were again noted.[51, 279, 564, 641] Changes in the blood picture before and after fever therapy were noted by Krusen; a characteristic "febrile hemogram" was seen: a postfebrile leukocytosis, an increase of polymorphonuclears and nonfilamented cells, later of monocytes, lastly of lymphocytes. The effects of experimental fever on human circulation (cardiac output, velocity of blood flow, blood volume) were studied (Moore and Kinsman).

Indications and contraindications for fever therapy were noted and were as given in previous Reviews.[497, 564, 613, 614, 703] Some described in detail the *management of patients during fever therapy.*[20, 25, 26, 75, 217, 497, 564, 597, 622, 641] To combat or prevent symptoms of anoxemia and oxygen deficiency during prolonged hyperpyrexia, Roth recommended the routine use of oxygen and carbon dioxide, the latter easily provided by "dry ice." A method for the continuous registration of rectal temperatures during fever therapy was described.[659]

Complications and Untoward Reactions. The types, incidence and management of minor complications of fever therapy (herpes, burns, headache, gastrointestinal symptoms, tetany) were again reviewed.[188, 217, 218, 279] Stecher and Solomon noted their incidence during 1000 sessions of fever given to 204 patients. One group of 142 patients with acute or chronic nongonorrheal arthritis, syphilis and various other diseases received 830 "mild treatments" (three to five hours at 103 to 105° F.). A second group of 62 patients with gonorrhea received 170 "severe treatments" (four to seven hours at 106 to 107° F.). The incidence of complications follows: nausea and vomiting accompanied 28 per cent of the mild, 36 per cent of the severe treatments. Burns accompanied 2 per cent of the mild, 14 per cent of the severe treatments. Herpes affected each group equally, 32 and 31 per cent of patients. However, anorexia and loss of weight were more common after mild than after severe treatments. Thus, anorexia accompanied 81 per cent of the mild, 65 per cent of the severe, treatments. Three patients in each group experienced the severe reaction of sudden uncontrolled

fever with mania, coma, circulatory collapse and shock—an incidence of 0.36 per cent of the mild treatments, 1.76 per cent of the severe treatments. There were no deaths but transient (10 days) right facial paralysis and aphasia affected one of the patients who received severe treatment.

Others noted serious complications, transient auricular fibrillation in two cases,[217] hematemesis in two cases,[217] heat collapse in three cases,[551] severe shock with recovery in six cases (but with death in two other cases).[388] Data on the major and fatal complications previously reported were reviewed by Humiston.

Eleven deaths related to fever therapy were reported during 1937 but this was in connection with many thousand sessions of fever. No deaths occurred during 1001 treatments of 189 gonorrheal patients of Potter, Redewill and Longley. Only one death occurred during about 2500 sessions of fever given by Parsons, White, Hardaway and Barnes; details of this death were not given. During 1500 treatments Epstein noted death of two severely paretic patients. Among 516 patients given 2580 treatments by Desjardins, Popp and Stuhler the mortality rate was 0.2 per cent: a girl with pelvic gonorrhea died after one session of fever. Warren, Scott and Carpenter treated 283 gonorrheal patients in six years with sessions of fever of varying lengths: only one death occurred, that of a young gonorrheal patient who died 26 hours after a long (24 hour) session of fever. Two additional deaths were reported by Wilbur and Stevens, two by Kopp and Solomon, one by Chunn and Kirkpatrick and one by Hartman. Findings at necropsy included the following: moderate dehydration of body tissues; cloudy swelling, early necrosis or parenchymatous degeneration of liver, vacuolar degeneration but no hemorrhages in adrenals; acute passive congestion of lungs with hemorrhages, softening of spleen, tubular or parenchymatous degeneration of kidneys, petechial hemorrhages of epicardium, myocardium, endocardium and kidneys; edema and hyperemia of intestines; subdural hemorrhages with cerebral necrosis, edema, congestion and cellular degeneration. To Wilbur and Stevens these findings markedly resembled those of fatal sunstroke. Kopp and Solomon considered the severe reactions of six patients who recovered and of two who died to represent true shock; its features were described. As a result of clinical and experimental studies of patients and animals Kopp and Solomon, and Hartman, regarded anoxemia as perhaps the chief cause of these complications; chief among the measures advocated for their prevention or control were administration of oxygen and carbon dioxide (e.g., by a nasal catheter), the avoidance of sodium amytal or adrenalin during sessions of fever. The use of caffeine was permitted by some [388] but condemned by others.[703]

Conclusions on the Merits of Fever Therapy for Gonorrhea and Gonorrheal Arthritis

Serious or fatal complications are rarely encountered when fever therapy is applied by a trained personnel. Although the mortality rate therefrom

is less than 0.2 per cent, the realization that death occasionally may occur from almost any method of treatment affords no consolation for the loss of a patient.[188] As one writer [116] put it: Assuredly such a potent weapon as fever therapy is not warranted against "small game syndromes." Gonorrhea and its complications are not small game and it has been amply shown that against them fever therapy provides a potent weapon. In spite of this its disadvantages are apparent. Pelouze regarded it incapable of universal use, "beyond the reach of the masses." Some patients are physically and emotionally unable to accept it.[111] Parran concluded, "While pyretotherapy may be effective in ordinary acute gonorrheal arthritis I believe that those who advocate its routine application for all such patients are inexperienced theorists. The incidence of acute gonorrhea is much too high and the technic of fever induction much too complex, costly and dangerous for general routine use."

[In the light of the results obtained from the use of sulfanilamide in cases of gonorrhea and its complications it would appear that fever therapy may be largely supplanted. In evaluating fever therapy it should be remembered that the work herein and heretofore reported was mostly done before sulfanilamide was available. Even though fever therapy may soon become outmoded, no one should discount the extremely valuable, highly scientific and courageous pioneer work of those who collaborated in its development. Although it is admittedly an heroic form of treatment, in its time it has constituted the greatest advance ever made in the treatment of gonorrhea and of certain other diseases as well. Nor should it be too hastily discarded; further comments will be made on the possible future rôle of artificial fever in treatment.—Ed.]

Sulfanilamide: Its Development and Its Use in Gonorrhea

The medical year 1937 might well be tagged "sulfanilamide year" for although the chemical, pharmacologic and experimental clinical background for use of the preparation had been well laid in the preceding five and more years, 1937 first brought wide clinical recognition. Seldom has any new drug aroused so much enthusiasm or so rapidly gained attention. "Much of this enthusiasm is warranted. The drug is truly remarkable." "Reports of its use are literally amazing. If the test of time bears out these early promises it will rank among the great therapeutic advances." So ran editorials in cautious medical journals.[204, 207] The development of sulfanilamide has a greater significance than many realize.[194, 420] Heretofore specific chemicals have been found for use only in nonbacterial diseases, those caused by protozoa (quinine and atebrine in malaria, arsphenamine, mercury and bismuth in syphilis; tryparsamid in trypanosomiasis, thymol and carbon tetrachloride for intestinal parasites). Until now no chemical specific has been developed for use in bacterial diseases (since optochin for pneumococci and chaulmoogra oil for leprosy have not yet gained clinical recognition as specifics). But the advent of sulfanilamide has established beyond all doubt that effective chemotherapy of microbial diseases is attainable. Because of this a brief outline of the development of sulfanila-

mide, as given by Hoerlein, Long,[420] Long and Bliss,[424] Welch and others, seems appropriate.

Discovery and Development. This will be given in summary:

1908. First description of para-amino-phenyl-sulfonamide—Gelmo.

1909–1910. Incorporation of sulfonamide grouping in azo dyes—Hörlein, Dressel and Kothe.

1913. Discovery of bactericidal properties (in vitro) of certain azo dyes—Eisenberg.

1919. Further work on bactericidal properties of azo compounds, including para-amino-phenyl-sulfonamide—Heidelberger and Jacobs.

1920. Existence of the dye compound later to be called prontosil was postulated by Bayer Company and Interessen Gesellschaft Farbindustrie.

1932. Prontosil synthesized by Mietzsch and Klarer, patented Christmas Day. Domagk, Director of the experimental pathological laboratory at Elberfeld, studied effects of prontosil on hemolytic streptococcal infections in animals; results seemed "too good to be true," hence he delayed publication until 1935. Meanwhile clinical reports began to appear.

1933. First clinical report: effect of prontosil ("streptozon") on staphylococcal sepsis—Foerster.

1934. Reports by Grutz: good effects of prontosil (oral) and "prontosil solution" (intravenous) in erythemas.

Veil noted beneficial effects of prontosil solution in "rheumatism."

1935. Good results from prontosil and prontosil solution in erysipelas—Gmelin.

First report (Domagk) of results of prontosil on experimental hemolytic streptococcic infections in animals.

Further German reports on the clinical effects of the prontosils on hemolytic streptococcal infections—erysipelas, puerperal fever, meningitis and certain other diseases including "infectious arthritis" (Klee and Römer, Schreuss, Anselm, Gantenberg, Imhauser, Bingold, Einhauser, Fuge, Roth, Schranz, Riecke, Scherber, Püschel); also on pneumococcal and staphylococcal infections (Recknagel).

French reports on effects in experimental diseases in animals—Levaditi and Vaisman; Nitti and Bovet.

Identification of colorless para-amino-benzene-sulfonamide as active agent in the dye compound prontosil by the Tréfouëls, Nitti and Bovet.

Favorable effects in gonorrhea—Schreuss.

1936. First French clinical report (Vermelin and Hartemann): use of "Rubiazol" (prontosil) in puerperal sepsis; oral preparation safe; intravenous preparation toxic.

Further French clinical reports on erysipelas and puerperal infections: Floch; Lemierre, La Porte, Laudat and Daum; Meyer-Heine and Huguenin; Bloch-Michel, Conte and Durel.

First English reports on the effects of the prontosils on experimental and clinical streptococcal and meningococcal infections—Colebrook and Kenny; Buttle, Gray and Stephenson.

Clinical and experimental work of Kramer, Hörlein, and Domagk.

Recognition of occasional serious toxicity—Colebrook and Kenny; Colebrook, Buttle and O'Meara.

Further studies on effects of prontylin in gonorrhea—Linser; Haugk.

1937. First and subsequent American reports by Long and Bliss on the effect of sulfanilamide on experimental and human beta hemolytic streptococcic infection.

Effect on pneumococcic infections: experimental (Rosenthal; Cooper, Gross and Mellon; Long and Bliss; Rosenthal, Bauer and Branham) and human (Heintzelman, Hadley and Mellon; Long and Bliss).

Effect on meningococcic infections: experimental (Proom; Proom and Buttle) and human (Schwentker, Gelman and Long; Long and Bliss).

Effect on experimental typhoid and paratyphoid B infections in mice—Buttle et al.

Effect on gonococcic infections: Grutz; Dees and Colston, Rueter and others.

Further results in various beta hemolytic streptococcal infections; puerperal sepsis (Foulis and Barr), scarlet fever (Peters and Havard), streptococcal meningitis (Gray; Causse, Loiseau and Gisselbrecht; Arnold; Schwentker et al.; Anderson; Weinberg, Mellon and Shinn, Douthwaite and others.)

Development of tests for quantitative determination of sulfanilamide in body fluids and studies on its absorption and excretion—Marshall, Emerson and Cutting.

Recognition of varied toxic reactions from sulfanilamide.

Further standardization of preparations and official approval of the term "sulfanilamide."

Preparations. The literature contains a confusing number of chemical and trade names for the various sulfonamide compounds. Some preparations, made for investigative purposes and described by full, not simplified, chemical terms have already been discarded as being more toxic or less effective than others. This discussion chiefly concerns the three main compounds used, to which many names have been given (table 1).

1. The first compound, made by Mietzsch and Klarer and used by Domagk, was a diazo dye, variously described as yellow, orange, red, brick red, or yellowish-red. It was 4-sulfamido-2′: 4-diaminoazobenzene, called "prontosil." It was first prepared in the form of a hydrochloride and was sparingly soluble. Later prepared as a base, it was completely insoluble in water. The red tablets were marketed as "prontosil," "streptozon," "rubiazol," "prontosil flavum" or "original prontosil." This preparation is no longer being promoted as later preparations were superior.

2. The next compound used was a prontosil solution, a soluble red azo dye for subcutaneous (not intravenous) injections. Neutral and easily soluble in water, it was the disodium salt of 4′-sulfonaminophenyl azo-1-hydroxy-7-acetyl amino-naphthalene-3: 6-disulfonic acid. It was called "prontosil solution," "prontosil soluble," "red prontosil" or "prontosil rubrum," and streptozon S. Unfortunately this form and not "original prontosil" was marketed in the United States under the term "prontosil" (Winthrop); this led to confusion and some called it "prontosil (American)" to distinguish it from "prontosil (European)." "Prontosil soluble" had the disadvantage of staining tissues somewhat red.

3. The Tréfouëls, Nitti and Bovet (1935) noted that prontosil and prontosil solution, though different in structure, had the same antibacterial action and each possessed the sulfonamide group attached to the azo group in the para position. Compounds with the sulfonamide group in the ortho or meta position were not potent. Therefore the antiseptic activity was

TABLE I

Sulfonamide Compounds

Original name	1. Prontosil (yellow or yellow red dye)	2. Prontosil solution (red dye)	3. Various names (white powder)	Some later compounds
Chemical name	4 sulfamido 2′, 4′ diamino azo benzene dihydrochloride	4 sulfamido-benzene 2′ azo, 1′ hydroxy 7′ acetylamino-naphthalene 3′ 6′ disodium sulfonate	para amino-phenyl sulfonamide or para amino benzyl sulfonamide	4—"*Diseptal A*": dimethylated di-sulfanilamide 5—"*Diseptal B*": monomethylated di-sulfanilamide 6—"*Diseptal C*": ("Di-sulfanilamide"; Disulon) a nonmethylated amide; para-amino benzene sulfonyl-para-aminobenzene sulfonamide 7—"*Proseptasine*" or "*Setazine*": para-benzyl amino benzene sulphonamide 8—"*Soluseptasine*": disodium para (gamma-phenyl-propyl-amino) benzene sulphonamide-alpha-gamma disulphonate.
Approved name (nonproprietary)			Sulfanilamide	
Synonyms or proprietary names	European prontosil Prontosil Prontosil I Original prontosil Prontosil flavum Rubiazol (4 different compounds) Streptozon Preparation 5214 (early European) Sulfamido-chrysoidine (French)	American prontosil Prontosil soluble Prontosil II Red prontosil Prontosil rubrum Prontosil S Prontosil (Winthrop) Streptozon S	Prontosil album (Bayer) Prontylin (Winthrop) P.A.B.S. (Hewlett) Stramid (Alba) Streptocide (Evans Sons Lescher & Webb) Colsulanyde (Crookes) Sulfamidyl (Abbott) Sulphonamid P (Burroughs Wellcome) (Allen & Hanbury) (British Drug House) Sulphanilamide (Boots) Sulfanilamide (Squibb) Deseptyl (Hungarian) 1162 F (French)	

apparently due to the para position of the sulfonamide group; that is, the azo linkage was unnecessary, the active principle being para-amino-phenyl-sulfonamide itself. This simplified compound was more soluble, less toxic and more effective than its more complicated predecessors. Para-amino-phenyl sulfonamide is also known as para-amino-benzyl sulfonamide or para amino sulfamido benzene. Various proprietary names were given to it: P.A.B.S., the initials of its chemical name (Hewlett); stramid (Alba Chemical Co.); prontylin (Winthrop); streptocide (Evans Sons Lescher and Webb); colsulanyde (Crookes); prontosil album (Bayer); sulfamidyl (Abbott); sulphonamid P (Burroughs Wellcome; Allen and Hanbury; British Drug House); sulphanilamide (Boots) and sulfanilamide (Squibb).

The British spell it with "ph," Americans with "f." Since it is the amide of sulfanilic acid the American Medical Association approved the nonproprietary term "sulfanilamide" which is now in general use.[112, 156, 157] Numerous manufacturers prepare it in 0.3 gm. (5 grains) or 0.5 gm. (7½ grains) tablets or in powder form (white crystalline substance) to be dissolved for parenteral injections. Since Marshall, Emerson and Cutting found that preparations injected subcutaneously do not produce concentrations in blood higher than oral preparations, hypodermic use of sulfanilamide seems to have little place except when its oral use is not practicable (patients in delirium or coma).

In summary, prontosil and prontosil soluble are not sulfanilamide but compounds which apparently break down in the body to liberate (rather small amounts of) sulfanilamide, their active principle. Now this active principle is used alone and in larger, more effective doses than are contained in prontosil or prontosil soluble.

Among numerous newer compounds synthesized to find preparations even more effective and less toxic are di-sulfanilamide (diseptal C or para-aminobenzene sulfonyl para-aminobenzene sulfonamide),[709] proseptasine, a benzyl derivative of sulfanilamide (para-benzyl aminobenzene sulphonamide), and soluseptasine or disodium-p-(gamma-phenyl-propyl-amino) benzene sulphonamide-alpha-gamma-disulphonate.[239]

In animals with experimental beta hemolytic streptococcal infections Barlow found sulfanilamide (prontylin) more effective than prontosil and he found disulon (or disulfanilamide) superior to sulfanilamide. Similarly Whitby found proseptasine much less toxic than sulfanilamide but equally effective. Soluseptasine (an injectable preparation) was less toxic than prontosil soluble but equally effective. Sulfanilamide was effective against experimental meningococcal infections but proseptasine and soluseptasine were not. Two experimental diaminobenzenesulfonanilide compounds possessed polyvalent action: one against streptococcus, pneumococcus and meningococcus, the other against streptococcus and pneumococcus.

[Such rapid advances are being made in the preparation and use of these related compounds that some of these data may be out of date when published. Therefore readers are obliged to consult the latest (1938) references on the value of newer preparations and the doses currently recommended.[58, 465]—Ed.]

Mode of Action. The original prontosil had only a slight antistreptococcal action in vitro but a strong effect in vivo (Domagk, 1935). Also prontosil solution had little effect in vitro but was potent in vivo (Colebrook and Kenny, 1936; Long and Bliss [422]). But sulfanilamide in a concentration of 1:10,000 was definitely bactericidal and bacteriostatic against certain bacteria in vitro as well as in vivo (Colebrook and Kenny, 1936; Colebrook, Buttle and O'Meara, 1936; Long and Bliss [421, 422]). Prontosil and prontosil solution were reduced in the body to form sulfanilamide. Perhaps prontosil and prontosil solution were, per se, relatively inert and effective only in relation to their quantitative reduction to sulfanilamide (Tréfouël, Nitti and Bovet, 1935; Colebrook, Buttle and O'Meara, 1936). This explanation,

however, does not satisfy those (e.g., Hoerlein) who have noted good results from sulfonamide compounds (e.g., diseptal C) which cannot be reduced to sulfanilamide in vivo, nor those who have obtained excellent results from amounts of prontosil solution which liberate only a few grains of sulfanilamide a day (Brown, Bannick and Habein). Perhaps sulfanilamide is not the main or only effective agent in these compounds.[79, 321] The mode of action of prontosil and prontosil solution is thus not yet known.

The mode of action of sulfanilamide is also obscure. Some (Levaditi and Vaisman 1935, 1936) suggested that it has a true bactericidal (antiseptic) action in vivo by preventing the capsule formation of streptococci, thus favoring natural phagocytosis. Some found no evidence of increased phagocytosis in animals treated with sulfanilamide.[709] Long and Bliss,[56, 421, 422] finding no evidence of any antiseptic effect of sulfanilamide in vitro (in the sense that phenol has), concluded that an effect other than bacteriostasis alone was involved; sulfanilamide inhibits growth of certain bacteria and injures them so that they can be markedly phagocytosed by leukocytes. Those interested further in theoretical discussions on the mode of action of sulfanilamide are referred to the reports of Bliss and Long, Mellon and Bambas, and Barron and Jacobs.

Absorption, Diffusion and Excretion of Sulfanilamide. Developing a method to determine concentrations of sulfanilamide in tissues and fluids Marshall, Emerson and Cutting studied its diffusion. Although the rate varies somewhat in different persons, absorption from the gastrointestinal tract is rapid and generally complete in about four hours. The drug then diffuses readily from blood to all body tissues and fluids where it is almost evenly distributed, concentrations in saliva, pancreatic juice and cerebrospinal fluid being only slightly less than that of blood. It takes two to three days to establish equilibrium between the amount ingested and the amount excreted; when administration of the drug is stopped, it takes two to three more days to free the system of it. By giving doses every four hours, concentrations in blood between 1:5000 and 1:10,000 can be readily attained and maintained as well by the oral as by the subcutaneous route. Therefore oral administration is preferable. Excretion is rapid and almost wholly via the kidneys, appearing in urine of man in a free and in a conjugated (acetylated), almost inactive form. Patients with impaired kidneys excrete it more slowly, therefore high concentrations in blood can be more rapidly attained. In such cases the drug must be administered with special care. According to Hill [317] the urine of patients excreting sulfanilamide has no bactericidal activity against beta hemolytic streptococci. But Helmholz and Osterberg and Cook and Buchtel noted that administration of sulfanilamide produces urine strongly bactericidal for the usual bacteria causing urinary tract infections except *Streptococcus faecalis.*

Pharmacology. The effects on animals were studied by Marshall, Emerson and Cutting, by Hawking, and by Hageman. Six grams of sulfanilamide per kilogram killed all, and 4 gm. per kilogram killed half, the mice tested. One gram per kilogram given to dogs produced nausea, vomiting, diarrhea, hyperpnea and neurologic symptoms resembling those of a decorticated dog. Sulfanilamide has almost no action on smooth muscle, heart or blood pressure. Animals which survived large doses showed no changes in liver, kidneys or other viscera. Animals which died from the drug had degenerative changes in the central nervous system. These facts hardly apply to human beings for lesions were produced in animals only by extremely large doses.

Toxicity of Sulfonamide Compounds. In general sulfanilamide and related compounds are either nontoxic or only mildly toxic. Toxicity affects ambulatory patients oftener than those in bed.[89, 419, 422, 424] Mild toxicity affects 50 per cent or more patients [335] being treated, producing malaise, tinnitus, dizziness, drowsiness, lassitude, anorexia, weakness, slight headache.[78, 79, 89, 419] In the presence of mild toxicity the same dose may be continued, or it may be reduced if the patient is not relieved by rest in bed.

Moderate toxicity produces the foregoing symptoms plus cyanosis (with or without sulfhemoglobinemia or methemoglobinemia), numbness and tingling of hands, face or feet, skin rashes, abdominal pain, diarrhea, fever, acidosis or a toxemia resembling that of ethyl alcohol. In such cases the dose should be reduced or administration stopped, or one may invite disaster.[79, 89] Signs of severe toxemia are collapse, fever, rapid pulse; leukopenia or agranulocytosis; hemolytic crises; jaundice. In such cases administration must be stopped and fluids forced. Sulfanilamide is soluble in water and readily excreted in urine. In acute toxicity, Long [419] sometimes prescribed 5000 c.c. water (oral) within 6 hours. Blood transfusions may be required in leukopenia or hemolytic crises.

In summary, sulfonamide compounds are relatively nontoxic for man although a serious reaction occasionally occurs. Among the 4000 reported patients so treated only 10 deaths, apparently related to the drug, have occurred (Mellon, Gross and Cooper); in five of them the drug may not have been the actual cause of death. There was apparently no correlation between the deaths and the dose used.

Sulfanilamide Fever. Rise in temperature (generally 101 to 104° F.; occasionally higher), may appear between the third and tenth day of treatment with repeated small doses or within 24 hours after a large dose.[135, 419, 421, 422, 669] If it occurs, use of the drug should be stopped for two to three days and the fever will disappear promptly. This fever must be distinguished from that of the primary disease. It may occur from one to five days after administration is stopped. Fever, with or without rash, affected 16 per cent of 134 patients of Hageman and Blake.

Gastrointestinal Symptoms. Nausea and vomiting not infrequently arise, sometimes with fever or intense headache,[315, 713] in one case with unconsciousness.[167]

Renal Symptoms. Generally these were not noted, although some considered irritability of the urinary tract common (Colebrook and Kenny 1936, Foulis and Barr). One of Reuter's patients noted marked slowing and weakness of urination.

Nervous System. This may be involved in animals receiving toxic doses but no comparable symptoms in man were reported, though Whitby had heard of one such case. Cokkinis noted loss of memory, deafness and headache once, loss of taste for tobacco and alcohol once. Mild choreiform twitchings affected an eight year old child.[630] One patient developed vertigo, nausea, dyspnea and loss of consciousness.[251] A patient of Bucy experienced severe reduction of vision and optic neuritis after taking 1 tablet of 5 grains (third course). [One of us, W. B., has encountered loss of memory, confusion, euphoria, loss of time sense.—Ed.]

Skin Rashes. These (with or without fever and sometimes severe enough for hospitalization) were frequently noted.[83, 236, 246, 261, 284, 285, 315, 335, 419, 469, 475, 490, 496, 513, 594, 601, 602] The rash was generally morbilliform or maculopapular, occasionally vesicular, erythro-edematous, hemorrhagic, urticarial or like erythema multiforme.

It generally appeared on face, trunk and extremities after 5 to 14 days of treatment. It affected 60 per cent of Schwentker and Gelman's cases. Once it appeared after the ingestion of 1 tablet of 5 grains.[601] If the rash is mild, treatment may be continued or the dose reduced. Rash and fever disappear within 48 to 72 hours after administration is stopped.[419] Salvin noted one case of diffuse urticaria, sneezing, lacrimation and dyspnea. Myers, Vonder Heide and Balcerski noted severe exfoliative dermatitis, edema, purpura, fever, marked leukocytosis and eosinophilia, acidosis and transient jaundice in a gonorrheal patient given 1325 grains (88.3 gm.) of sulfanilamide in 28 days.

In some cases the factor of photosensitivity was noted, lesions appearing only on parts exposed to sun. The lesions were urticarial, erythematous, macular, maculopapular or vesicular.[83, 469, 496, 513] Brunsting noted excess porphyrinuria in two such cases. Patients taking the drug should avoid undue exposure to sun.

Acidosis. Most patients develop a fall (average 14.1 volumes per cent) in the CO_2 combining power of blood; a few develop clinical acidosis—air hunger without ketonuria.[419, 424, 640] The cause of the phenomenon is not clear but there is an increased urinary excretion of sodium and potassium. Intravenous or subcutaneous injections of ⅙ molar sodium lactate solution will correct it.[38, 424] To prevent it 10 grains of sodium bicarbonate are given with each dose of sulfanilamide by some physicians.

[In view of more recent work the question of the production or prevention of acidosis should be considered unsettled. Some doubt that such small doses of alkali are effective. Indeed some now regard the use of alkalis contraindicated.—Ed.]

Leukopenia. This was occasionally noted with depression of myeloid elements.[424, 530] Since sulfanilamide contains the benzene ring it may affect the hematopoietic system.

Acute Hemolytic Anemia. This, frequently with jaundice, was noted in 15 cases.[299, 347, 386, 424, 705] It was nonfatal but transfusions were often necessary. Its mechanism is unknown. Estimations of hemoglobin and differential blood counts should be made every two to three days to obtain forewarning of hemolytic anemia. If the hemoglobin or erythrocyte counts are notably reduced, administration of the drug should be continued only with great caution.[420] Jaundice may accompany toxic hemolytic anemia or agranulocytosis.

Agranulocytosis. This was noted 10 times; it was fatal in 7 cases.[63, 194, 347, 424, 425, 459, 475, 547, 747] It occurred after prontosil, prontosil solution, sulfanilamide and proseptasine. The mechanism of its production differs from that seen in the agranulocytosis due to amidopyrine.[424]

Sulfhemoglobinemia and Methemoglobinemia. These conditions may complicate sulfanilamide therapy. To the three cases of sulfhemoglobinemia earlier reported by Colebrook and Kenny (1936) can be added about 13 more cases,[18, 135, 190, 244, 419, 527] one of which was fatal.[249] Sulfhemoglobinemia was not noted among the 235 cases of Peters and Havard and Whitby. The condition may represent an idiosyncrasy as its appearance seemed unrelated to the dose used.[249] Although it may occur in patients to whom sulfates have not been given [419, 422,527] the latter supposedly predispose to it. Therefore, during and for two or three days before sulfanilamide therapy, patients should *not* be given magnesium sulfate dressings, magnesium sulfate or other related saline cathartics. One must also avoid licorice powder (or other drugs containing sulfates), the anthracene group of aperients, aniline dyes (phenacetin and acetanilid), phenylhydrazine derivatives, amidopyrine, sulfonal, methylsulfonal.[190, 239, 709] To prevent sulfhemoglobinemia Archer and Discombe also prescribed preliminary colonic enemas and, during treatment, the use of a low residue diet poor in sulfur, and 30 to 45 c.c. liquid paraffin daily. When sulfhemoglobinemia occurs cyanosis may be spectacular and alarming but not serious if use of the drug is stopped. One should not look only for cyanosis but should check the patient's hemoglobin every four days.[190]

After administration is stopped sulfhemoglobinemia may last six weeks; methemoglobinemia lasts only about 24 hours.[527] Previously noting sulfhemoglobinemia, Long and Bliss [425] later were uncertain of the accuracy of their spectrophotometric readings and were not sure whether true sulfhemoglobinemia really occurred.

[In patients receiving full doses of sulfanilamide cyanosis practically always appears in 8 to 12 hours after the initial dose and may be present for two to four days before met- or sulfhemoglobinemia can be detected. However the latter are rarely the causes of cyanosis in our experience; cyanosis is produced in some other manner. —Ed.]

Methemoglobinemia and cyanosis were noted in 50 per cent of Hageman's 60 patients on sulfanilamide. Seven other cases were noted.[18, 46, 527, 662] It occurred in patients who were receiving generally large doses of sulfanilamide,[527] but sometimes small doses.[46]

Cyanosis. Mild to marked cyanosis occurs in 75 to 90 per cent of patients using sulfanilamide.[419, 425] Cyanosis alone is no contraindication to continued treatment. It may occur with sulfhemoglobinemia or methemoglobinemia but before assigning the cause one must examine the blood spectrophotometrically. Slight cyanosis and tachypnea may arise with acidosis.[422] Archer and Discombe saw it due to coincident pneumonia, and to overdosage of paraldehyde. The cause of the cyanosis is not known; it is rarely due to sulfhemoglobinemia or methemoglobinemia, according to Marshall and Walzl but may be due to the presence of a black oxidation product of sulfanilamide which stains erythrocytes. Even in cases of deep cyanosis blood lactic acid was not significantly increased.[88]

It is widely known that the deaths from elixir of sulfanilamide—Massengill were due not to sulfanilamide but to the solvent used—diethylene glycol. Discussion of this tragic incident is unnecessary here.[113, 114]

Sulfanilamide for Gonorrhea and Gonorrheal Arthritis.—In the United States the effect of sulfanilamide on gonorrhea was first reported in May 1937 by Dees and Colston and by Reuter but in Germany previous work had been done. The beneficial effects of prontosil used alone or with orthodox remedies in males and females with gonorrhea had been noted by Schreuss (1935), Linser (1936) and Haugk (1936). Others (Ehlers 1936, Becker 1937) noted no results from prontosil. In May 1937 Dees and Colston treated 19 patients with gonorrhea (none with arthritis) most of whom received daily (in four divided doses) 4.8 gm. of sulfanilamide for two days, 3.6 gm. for three days and then 2.4 gm. for four to eight more days. In 12 cases urethral discharges stopped in one to three days and smears became negative in two to five days. A few cases were more resistant: "Three or four were little if any benefited." [Further experience indicates that these doses were inadequate for all cases.—Ed.] In May and November 1937 Reuter reported results from sulfanilamide in 100 cases of gonorrhea of all degrees and stages. Patients received 40 grains daily for apparently only three days. Rapid recovery resulted in 90 per cent of the 100 cases, generally within five days; in 93 per cent of the 40 acute cases, in 88 per cent of 60 chronic cases (over two weeks' duration). [It is interesting to note the percentage of cures among these patients given doses now considered inadequate.—Ed.] Side-effects of the drug were often noted; those who "complained early and bitterly" of them responded best; those who did not respond apparently tolerated the drug. Of the series none had

arthritis but in a new series (to be reported) was one case of gonorrheal arthritis which showed "astonishing improvement."

In December Colston, Dees and Harrill reported further experiences. Results were successful in all but 10 (16 per cent) of 62 cases of genitourinary gonorrhea (none with arthritis). Sulfanilamide was given longer than previously and in a little greater dosage: first two days, 5.3 gm. (80 grains); next five days, 4.0 gm. (60 grains); next seven days, 2.7 gm. (40 grains); next 14 days, 1.3 gm. (20 grains) in each case daily. Recurrences occurred only when smaller doses were used or when treatment was prematurely stopped. Records of 10 patients with gonorrheal arthritis treated by colleagues were reviewed. The average duration of these cases was 19 days, excluding one case of two years' duration. Joint pains disappeared after an average of two days and joint swelling after an average of 13 days from the onset of sulfanilamide therapy. Buchtel and Cook, and Douthwaite each noted "dramatic recovery" in one case of gonorrheal polyarthritis. Among 250 patients with gonorrhea treated with sulfanilamide by Cokkinis were an unstated number with gonorrheal arthritis or fibrositis, most of whom "reacted quite well" (details not given). In most cases, uncomplicated acute and chronic urethritis cleared up rapidly and completely but in cases of acute prostatovesiculitis, with or without epididymitis, there often was great resistance to treatment. Many were given local treatment as well as sulfanilamide, the latter generally in doses of 3 to 5 gm. daily for two to seven days; thereafter, as necessary, 3 gm. daily for seven more days and 1.5 gm. daily for seven more days. "We now possess an effective remedy for gonorrhea and for most of its complications." Cokkinis recommended a total dose of not more than 60 to 70 gm. in three weeks.

Other reports noted the effect of sulfanilamide or related drugs in cases of gonorrhea without arthritis. Herrold noted results in 30 cases: in 10 (83 per cent) of 12 cases, chronic gonorrhea was cured in 7 to 21 days; but in only 1 (25 per cent) of 4 subacute cases and in only 4 (28 per cent) of 14 acute cases was a cure effected. Doses of sulfanilamide were small, however, generally 20 to 45, rarely 80, grains daily. The use of 30 to 40 grains of sulfanilamide daily proved "almost a specific" in most of Branham's (unnumbered) cases. The acute discharge was "invariably relieved" but the "spectacular" results led to a false sense of security as prostatitis often persisted when treatment was prematurely stopped. Of Buchtel and Cook's 31 patients, 27 (87 per cent) were promptly cured within one week, 4 had symptoms after one week of treatment. In those cured, recurrences were not noted in spite of repeated examinations. The general plan of dosage was 60 to 80 grains (4 to 5.3 gm.) daily for two days, then 40 grains (2.6 gm.) daily for about 10 days more. Even when clinical cure of gonorrhea was noted early, 20 grains (1.3 gm.) daily was given for 10 to 14 more days. This plan was not routine: some patients must start on a small dose and gradually increase it; others noted good results on a small daily dose; about 10 per cent of patients could not take the drug at all. To reduce symptoms of toxicity it was recommended that patients remain in bed the first two or three days of treatment.

Carey treated two patients with acute vulvovaginitis, with small doses of sulfanilamide (20 to 45 grains daily): One was cured; one was not. Anwyl-Davies treated 19 acute cases with small doses of sulfanilamide; results were "distinctly dis-

appointing"; later, 20 patients were treated with larger doses (4.8 gm. daily for two days, 3.6 gm. daily for three days, 2.4 gm. daily for four to eight days). Results were still "unsatisfactory"; the drug was considered "ineffective." These poor results were promptly challenged by others. Excellent results (not statistically analyzed) were noted by Erskine, Johnson and Lloyd in treatment with larger doses (those used by Dees and Colston) of 100 patients with gonorrhea. Treatment with prontosil soluble and sulfanilamide, combined with irrigations, proved rapidly effective in 90 of Crean's 100 cases of acute and chronic gonorrhea. Patients who did not respond within 18 days were not likely to respond at all. Thirty patients with gonorrhea were treated by older methods; it took three times as long to cure them as to cure patients treated with sulfanilamide.

Orr treated 134 patients: 91 (88 per cent) of 104 males and 26 (87 per cent) of 30 females were cured generally within one to five days, 25 patients within 5 to 15 days. Dosage of sulfanilamide was 80 grains daily for four days, 40 grains daily for four more days, 20 grains daily for seven more days. According to Brown, Bannick and Habein, at least 90 per cent of male patients and 80 per cent of female patients with gonorrhea "adequately treated" with sulfanilamide were cured. At first, 75 to 90 grains daily (in six divided doses) was given until a concentration of 8 to 10 mg. per cent was established. When definite improvement was noted the dose was reduced to 60 grains daily (given in four divided doses); with further improvement it was reduced to 50 grains daily and continued if necessary for three to four weeks. Among those cured was a woman previously unimproved by repeated fever therapy and prolonged local treatment. Of 72 patients treated by Watts, Oden and Gordon, 45 (63 per cent) were "cured" or "apparently cured"; 13 (18 per cent) were improved; 14 (19 per cent) were unimproved. Dosage was 80 grains daily for two days, 60 grains daily for three more days, 40 grains daily for nine more days.

Results were satisfactory in 88 per cent of Humiston's 100 cases, unsatisfactory in 12 per cent. Patients were given sulfanilamide, 45 grains daily for two days, 30 grains daily until gonococci were no longer found, and 15 grains daily until a provocative course was completed. The latter consisted of daily prostatic massage, instillation of silver nitrate and final injection of gonococcus vaccine: if gonococci were not found thereafter the patient was believed cured. A child with gonorrheal vulvovaginitis was cured by McCullough.

Method of Administration. Since results from sulfanilamide are dependent on its adequate concentration in blood, a rational and successful method of treatment is the administration of relatively large initial doses followed by smaller doses sufficient to maintain an adequate concentration of the drug in the blood (1:10,000 concentration = 10 mg. sulfanilamide per 100 c.c. blood). Long and Bliss [419, 421, 424] therefore recommended, during the first 24 hours, the oral use of 5 gm. sulfanilamide (or 1 gm. for every 20 lbs. or 9 kg. [*i.e.* ¾ grain per pound] body weight) or 120 c.c. of prontosil soluble (2.5 per cent solution; 1 c.c. for each pound of body weight).

Their general plan of dosage follows:

1. Dosage of sulfanilamide orally for patients weighing over 100 lbs., a total dose of 50 to 80 grains in the first 24 hours, followed by a maintenance dose of 15 grains every 4 hours; for patients weighing 50 to 90 lbs., a dose of 30 to 50 grains in the first 24 hours and 10 to 15 grains every 4 hours thereafter; for children weighing 25 to 50 lbs., a dose of 20 to 30 grains during the first 24 hours and thereafter 5 to 10 grains every 4 hours.

Since patients absorb and excrete the drug variably, doses may vary and they are controlled by estimating the concentration of sulfanilamide in the blood by the method of Marshall, Emerson and Cutting, 4 hours and 24 hours after the initial dose.

2. Dosage of parenteral sulfanilamide solution. Doses follow: For persons over 100 lbs. in weight an initial hypodermoclysis of 500 c.c. of a 1 per cent solution, thereafter two doses of 300 c.c. each at 8 hour intervals; for persons weighing 50 to 90 lbs. an initial dose of 200 to 400 c.c. followed by 200 c.c. at 8 hour intervals; for children weighing 25 to 50 lbs., an initial dose of 100 to 300 c.c. followed by 100 to 200 c.c. at 8 hour intervals. Babies should receive a total of about 1 gm. of sulfanilamide per 10 lbs. of body weight during the first 24 hours. The simple method of preparing sulfanilamide powder for parenteral injection was given [157, 424]: Dissolve the sulfanilamide powder in sterile physiologic saline solution (0.8 to 1 gm. sulfanilamide to each 100 c.c. saline solution). Heat to 90° C. until solution accomplished; then cool to 37° C. and inject at that temperature. If it cools below 37° C. the drug will crystallize out.

3. Dosage of prontosil solution (parenteral). Directions follow: For persons over 100 lbs., 20 c.c. at four hour intervals (six injections the first 24 hours); for persons weighing 50 to 90 lbs., 10 to 15 c.c. every four hours; for children weighing 10 to 50 pounds, 5 to 10 c.c. every four hours until a definite clinical effect is noted; then the dose should be gradually decreased.

Since, theoretically, 100 c.c. of prontosil soluble (2.5 per cent solution) yields only 0.73 gm. of sulfanilamide, a great disproportion in the recommended amounts of these two drugs is obvious.

4. Summary. Of those who treated gonorrhea and gonorrheal arthritis as noted, several used doses approximating those recommended by Long and Bliss; others used smaller doses, in general with less success. With experience, the tendency was to use larger and more effective doses. The exact value of the drug in gonorrhea will not be determined until physicians have studied more patients treated by full doses so that adequate concentrations were attained and maintained.

[To attain rapidly and maintain an adequate concentration of sulfanilamide one of us, W. B., has adopted the following plan of dosage: (1) a daily dose of ¾ grain sulfanilamide per pound body weight; (2) on the first day, large single doses to attain proper concentration rapidly; an initial dose equal to the total calculated dose for one day, or half as large a dose at the initial dose and a similar dose four hours later; (3) thereafter, to maintain a constant blood level give ⅙ the full calculated dose every four hours *day and night;* (4) fluid intake should be constant to maintain a constant blood level. *Example:* For a man weighing 160 lbs. the full daily dose of sulfanilamide would be 120 grains. The initial dose would be 120 grains (or 60 grains and another 60 grains in 4 hours); thereafter grains 20 every 4 hours day and night.—Ed.]

To prevent or anticipate significant toxicity the following were recommended: Instruct patients to avoid excess exposure to sun. Avoid sulfur containing compresses or drugs. Estimate the hemoglobin concentration and differential blood count every 2 to 3 days. Give 10 grains of sodium bicarbonate with each dose of sulfanilamide; this may help prevent gastric symptoms. Keep the patient in bed at least the first two to three days of treatment. In the presence of renal insufficiency test the concentration of blood sulfanilamide daily and stop administration if the concentration reaches 15 to 20 mg. per cent. With signs of minor toxicity force fluids; use of the

drug may not necessarily have to be stopped; the dose often can be continued or lowered. If patients are doing well, do not discontinue use of the drug prematurely. When major toxicity is apparent or feared, administration should be stopped at once and fluids forced.

[More recently patients have been treated with concentrations as high as 40 mg. per 100 c.c. blood. Only under special conditions should fluids be forced; this would lower the blood concentrations.—Ed.]

Obviously, sulfanilamide is most useful but occasionally is dangerous, and should be used only under a physician's supervision. On prescriptions should be written: "Do not refill." [569] In too many stores laymen can purchase the drug freely over the counter and a salesman may recommend the dosage. In such cases untoward effects will too often occur; steps must be taken to prevent misapplication of the drug.

Sulfanilamide Combined with Fever Therapy. Because of its toxicity, sulfanilamide cannot be taken in effective amounts by some patients; others may be infected with strains of gonococci unusually resistant to sulfanilamide. Therefore sulfanilamide will fail to cure a certain percentage of patients (10 to 15 per cent according to Buchtel and Cook). In some of the latter cases sulfanilamide, combined with fever therapy, may be effective. Results of this combination were successful in treatment of all of 10 patients who were resistant to sulfanilamide or to fever therapy alone, given by Ballenger, Elder and McDonald, who concluded that the remedies together were more effective than either alone. Sessions of fever of only 3 to 4 hours at only 103 to 104° F. were reputedly sufficient. Their plan of treatment had not yet been standardized and was not clearly stated. Eighty grains (5.3 gm.) of sulfanilamide were given daily for one or two days; a session of fever was given the next day, with 60 grains of sulfanilamide that day, and 60 or 80 grains the day after the fever. Use of the drug was then continued (60 grains daily) while two more sessions of fever were given, one every other day. Some patients were cured by only two or three days of sulfanilamide and one session of fever; others required three or four sessions of fever and several days of administration of the drug. This treatment may be indicated not only in resistant cases but for patients who urgently need an immediate cure for domestic or economic reasons.

Sulfanilamide plus fever therapy was also used by Cheetham and Roemer in treatment of 12 patients resistant to the drug alone: all were cured within 10 days. The program was that of Ballenger, Elder and McDonald except that the drug was administered (40 grains daily) for a total of 14 days. There were no recurrences.

[Three of us, W. B., M. H. D., and P. S. H., have also noted successes with this combination in the presence of resistance to the drug alone. But the combination is not always successful. Before considering results from the drug alone to be a failure, one must be sure that the "failure" is not due simply to an inadequate concentration of blood sulfanilamide from insufficient dosage or failure to keep fluid intake constant. The combined method seems indicated primarily if the disease is

truly resistant to full doses of the drug or if patients are tolerant of only small doses. —Ed.]

Older Forms of Treatment. In view of recent developments, the "older methods" seem outmoded but some will wish to compare their effects as controls on newer methods. Massive doses of gonococcus vaccine given subcutaneously were considered by Drummond effective in 28 cases of gonorrhea with and without arthritis. "Major shock," including fever (103 to 104° F.) was produced. Urethral discharge lasted (after treatment was begun) 3 to 14 days in the vaccine-treated group, 43 to 240 days in 14 controls treated by other methods. Specific antigonococcal serum therapy was "not very successful": Keefer and Spink were able to increase the bacteriolytic titer of serum thereby and clear the blood in some cases of bacteremia, but intra-articular injections of serum were ineffective. Goldey considered autoserotherapy advantageous. [We cannot agree.—Ed.] Anwyl-Davies treated 157 male patients, including 31 with arthritis, with a specific antitoxin or gonococcal filtrate. Results were "excellent" in 49 per cent, "good" in 30 per cent, "fair" in 15 per cent, "bad" in 6 per cent. Acute arthritis often was notably improved in a week; chronic arthritis within two to three weeks, but local genital lesions took 4 to 12 weeks to heal. The Corbus-Ferry filtrate seemed to Wishengrad of no value in acute gonorrheal urethritis, of possible value in chronic cases. Only 12 of Whitehouse's 30 patients were "cured" with this filtrate. Use of a bacteriophage or gonococcal (and mixed bacterial) lysate called "Neisso-jel" (Lilly) was condemned as dangerous by Brunet and Salberg. Robinson treated an unstated number of patients with gonorrheal arthritis with intramuscular injections of chaulmoogra oil; "excellent results were obtained in every case." Among patients treated with gold by Hartfall, Garland and Goldie were six with gonorrheal arthritis: one was "cured," two markedly improved. No conclusions were drawn.

Roentgenotherapy for gonorrheal arthritis was strongly recommended by Kahlmeter. However, results of treatment in 100 cases were not statistically analyzed: "At least 90 per cent of patients recover completely provided they come for treatment sufficiently early." Apparently Kahlmeter frequently used fever therapy also, considering the combination superior to fever therapy alone. [We have not been impressed with the results of roentgenotherapy in a small group of cases of gonorrheal arthritis.—Ed.] After aspiration of gonorrheal joints, the instillation of air "to distend joint surfaces, relieve pain, and aid in preventing deformities" was advised by Bohlman and Rombold. [One of us, A. J. K., has used this without success.—Ed.]

There appeared a number of reports on the standardization of older methods of treatment of gonorrhea of males and of females.[42, 67, 144, 182, 192, 228, 444, 471, 478, 488, 493, 536, 537, 538, 560, 568, 711, 727, 732, 733, 734] Marshall discussed the incidence and treatment (by old methods) of gonorrhea in pregnancy. Elliott treatments are contraindicated in acute cases but may be helpful in chronic cases of pelvic gonorrhea for which fever therapy may be imprac-

ticable; of 45 patients so treated by Randall and Krusen, 55 per cent were cured, 22 per cent improved.

The next few papers are reviewed, not because of their therapeutic value but because they describe certain interesting physiologic observations which, in spite of more dramatic current discoveries, may still be of more than academic interest.

Gonorrheal vaginitis of children is common and may occur at any age from birth to puberty; however, it is rare during the first few weeks of life and rare among adults. During the first five weeks of infancy, and again from puberty to the menopause, the vaginal epithelium is thick (30 to 40 layers of cells) and rich in glycogen, and the vagina is decidedly acid in reaction. From the fifth week of life until puberty the vaginal epithelium is thin (6 to 12 cell layers deep) and less rich in glycogen, and the vagina is alkaline (pH 7.0 to 8.0). Bumm (1885) observed that gonococci cannot invade intact squamous epithelium but have a distinct predilection for columnar epithelium; only the latter type of epithelium succumbs to gonococcal invasion. Gonococci do not attack the acid adult vaginal epithelium and are rarely found in vaginas of infants under three to five weeks of age. The blood of newborn children is rich in estrogen (acquired from the maternal circulation during pregnancy) for a short time only, then this substance rapidly decreases in amount. Perhaps newborn infants are protected from gonorrheal vaginitis because their blood is rich in estrogen and their vaginal epithelium is thick as in adults (Allen and Diddle, 1935). Allen (1928), Lewis (1933) and others noted that a thick-celled postnatal or adult type of vaginal epithelium (with acid vaginal reaction) could be induced in children by theelin (estrin, amniotin) when given hypodermically or in vaginal suppositories, but not when given orally. Lewis (1933) and others therefore administered estrogenic substances in cases of juvenile gonorrheal vaginitis in order to induce a metaplasia of vaginal mucosa which might be antigonococcal. Considerable success was attained although recurrences were frequent.[47, 49, 186]

Berry's results with theelin in 25 cases of juvenile gonorrheal vaginitis (15 acute, 10 chronic) were: cure in 68 per cent, temporary control in 28 per cent (recurrences later), failure in 4 per cent. In acute cases an average of 12,000 international units were given in an average of 56 days; in chronic cases, a total average of 8500 international units over an average of 34 days. The recommended dose was 1000 international units of theelin triweekly until the patient was symptomatically and bacteriologically cured. Sacher obtained good results from amniotin vaginal suppositories: one each night for three weeks, then one twice a week for three weeks.

Injections of estrin (1000 to 2000 international units) will also effect epithelial hyperplasia and metaplasia in the urogenital tract of male monkeys (Van Wagenen 1935; Deming, Jenkins and Van Wagenen). Hence estrin therapy might be of value also in gonorrheal urethritis of males. Intragluteal injections were given every one or two days. No results were noted in 12 patients given 2000 to 4000 international units within 20 days, or in 3 patients given 48,000 to 86,000 units in 13 to 16 days. Two patients given 88,000 and 92,000 units within 17 days were cured, within 10 days, of admittedly "slight" urethritis.

Recently Hall and Lewis (1936) and Karnacky (1936) concluded that the histologic changes of vaginal epithelium were not directly but indirectly responsible for gonococcal destruction. When theelin was given, the vaginal secretions generally became definitely acid (pH 5.9 to 5.0 or lower). Vaginal smears never became negative until the pH was 5.5 or less. Cures occurred only when theelin produced an adult (i.e. acid) vaginal pH. Theelin greatly increases vaginal cells which contain glycogen. As these cells break down, lactic acid is produced from the glycogen, forming an acid secretion which destroys gonococci as they cannot live at a pH

greater than 6. Why not therefore acidify the vaginal mucosa in a simple, less expensive way than by endocrines? Karnacky treated about 200 patients with juvenile gonorrheal vulvovaginitis, using acidulated sugar tablets. Results were as good as those from ovarian hormone. Using a somewhat similar glucose tablet, Little also reported good results. Karnacky also obtained good results by "a new hormone method": 40 to 100 c.c. of citrated blood, very rich in hormones, obtained from pregnant women, were injected intragluteally every day for 4 to 5 days or until the children's vaginal secretions changed from alkalinity to an acidity of pH 5.5 or less to nitrazine paper. Marked vaginal metaplasia and acidity of vaginal secretions resulted and smears became promptly negative for gonococci and remained so.

An interesting report on the history of gonorrhea was made by Brodny.

Tuberculous Arthritis

The general features of tuberculous arthritis were reviewed (Kleinberg; Seddon). It is still common and affected 22 per cent of the 4626 orthopedic patients in the Hospital for Joint Diseases, New York, during 1934 and 1935. Seddon described four clinical stages: 1. In the stage of invasion, physical but not radiographic evidence of arthritis is present. It usually lasts for a few weeks or months. [Occasionally 1 to 3 years.—Ed.] 2. The first stage passes into the stage of tissue destruction, lasting several months, in which radiograms reveal involvement of soft tissue, cavitation and absorption of cartilage. Destruction is due partly to the disease, partly to mechanical factors. 3. In the stage of quiescence the joint is no longer swollen, and serial radiograms show no further destruction of bone but healing has not occurred and the focus still contains many bacilli. 4. In the stage of healing the joint is painless and not swollen. Bone trabeculae reveal more calcium; joint surfaces are more clearly defined. Tuberculous granulation tissue is converted into fibrous tissue in which tubercle bacilli may persist for years. Fibrous ankylosis develops, on the strength of which depends the safety of the joint.

The features of tuberculosis of hip, spine, knee, ankle, shoulder, elbow and wrist were reviewed.[380, 607]

Tuberculous Spondylitis. This is the commonest form of tuberculous arthritis. When cervical or lumbar vertebrae are affected symptoms generally precede objective or roentgenographic evidence of disease; the reverse is true when thoracic vertebrae are affected (Kleinberg). Over a period of 17 years Cave studied 122 cases in children. Pulmonary tuberculosis affected 60 per cent. The disease may first affect the intervertebral disk (especially in the lower thoracic or lumbar region), the center of the vertebral body or (most often) its anterior border. Lesions were cervical in 5 cases (4 per cent), thoracic in 94 (77 per cent), lumbar in 19 (16 per cent) and lumbosacral in 4 (3 per cent). Commonest complications were abscess, which afflicted 75 per cent, and paraplegia which afflicted 6.5 per cent (9 patients); of the latter, 4 patients died. Tuberculous joints rarely become fused spontaneously unless there is marked secondary infection. However, in six cases spontaneous intervertebral fusion occurred. Twenty-five pa-

tients had tuberculous arthritis elsewhere. Of the 122 patients 19 (16 per cent) died, eight of them with amyloidosis.

Severe trauma is a rare; mild or moderate trauma is a not uncommon, predisposing factor in Pott's disease (Skolnick). Adams and Decker described some unusual sites of primary tuberculosis in the spine: lateral articulations, spinous processes, and between the head of a rib and the vertebral body.

Diagnosis of Tuberculous Arthritis. The following are helpful in diagnosis: a family history of tuberculosis, evidence of preëxisting or coincidental nonarticular tuberculosis, a history of trauma or recent acute infection which may have acted as a precipitating factor, the location of the lesion (temporomandibular involvement is rarely tuberculous; monarticular affections of spine, hip, or knees are likely to be tuberculous) (Kleinberg).

Roentgenograms. Clear roentgenographic evidence of tuberculous arthritis may be long absent. At necropsy vertebral bodies are often found completely involved, without previous roentgenographic signs thereof (Adams and Decker). Ferguson likewise concluded that there is no formula for the roentgenographic diagnosis of tuberculous arthritis: "The [roentgenographic] differentiation of tuberculosis from other infections is a matter of perceiving the characteristic expression of chronic and progressive development of effusion, soft tissue atrophy, decalcification, and thinning of cartilage space without productive calcifying reaction." The roentgenologist must have a knowledge of the history and clinical features to help him interpret roentgenograms properly in this disease.

Blood chemistry. As would be expected with a purely destructive bone lesion, Mitchell and Crawford found no elevation of serum phosphatase activity in juvenile or adult tuberculous arthritis. There was no correlation between the activity or stage of disease and the phosphatase level.

Treatment. Principles of treatment were reviewed (Kleinberg, Cave, Seddon). The value of rest, heliotherapy, dietotherapy and conservative nonsurgical treatment, especially for children, was emphasized. Prolonged rest is required for patients in bed when weight bearing joints are involved. For wrists or elbows simple fixation may suffice; for other joints traction is usually required. Traction or hyperextension should be discontinued when bone destruction stops. To favor ankylosis joint surfaces must not be separated too long; they should be allowed to fall together after three consecutive radiograms taken four months apart show cessation of bone destruction with recalcification and articular "clearing" (disappearance of fluffy outline). When the joint begins to heal and ankylosis begins, supports are needed to protect the "young ankylosis." Fixation operations may then be valuable.[607] [Many still believe that much time and some lives can be saved by early fusion.—Ed.]

Optimal local treatment varies for different joints and ages. Cave and Kleinberg favored prolonged conservative treatment (long immobilization on a convex hyperextension frame) in cases of juvenile Pott's disease.

Fusion was done in 29 of Cave's 122 cases after an average of three years of preliminary conservative treatment; results were satisfactory. No operations, he said, should be done during the acute stage of the disease or during hot summer months. [Some believe that, when necessary, operation at those times is permissible under local anesthesia.—Ed.] Haas, however, favored spinal fusion in children, done as soon as possible, generally within a month of the patient's admission to the hospital. Good results were so obtained in treatment of 80 per cent of 60 patients. In adults Kleinberg favored early spinal fusion but Seddon recommended prolonged conservative treatment prior to fusion. For affected hips prolonged immobilization, then fusion, were favored.[380, 607] For affected knees, shoulders, elbows and wrists of children conservative treatment by immobilization was advised; for adults, early arthrodesis usually seemed preferable although occasionally good results were obtained in elbows by excision and pseudarthrosis.

Fusion was performed by Tregubov in treatment of 147 of 609 patients with tuberculous knees, never in children under eight, rarely in those under 15 years of age, then only after prolonged conservative treatment. Amputation was necessary in five cases; two patients died; other results were quite satisfactory.

Pneumococcal Arthritis

Pneumococcal arthritis is rare. During 25 years at The Hospital of the Rockefeller Institute only two cases (1 of type I, 1 of type III pneumococcus) were noted in about 1800 cases of pneumonia (Chickering). When present it usually accompanies pneumonia, occasionally pneumococcal septicemia without pneumonia. Usually a monarthritis, a knee is likely to be affected; less often a shoulder, wrist or elbow. When joints are aspirated for diagnosis smears and cultures should be made. Early cultures may be negative; repeated aspirations may be needed for diagnosis. Most patients are critically ill, often with other complications, and often do not survive. When they do, complete articular function usually is restored. However, cartilage and synovial destruction may result unless joints are aspirated and drained surgically.

A new treatment may now be available, as sulfanilamide seems effective against certain types of pneumococci, especially type III (mucosus), according to the following reports.

This was first noted in animal experiments by Domagk (1935, 1936) and by Buttle, Gray and Stephenson (1936). Recent studies on the effect of sulfanilamide on experimental pneumococcic infections were those of Rosenthal, Rosenthal, Bauer and Branham, Gross and Cooper, Cooper, Gross and Mellon and Long and Bliss. Inhibition of pneumococci type I in vitro was noted by Buttle, Parish, McLeod and Stephenson. A few patients with type III lobar pneumonia were favorably affected by sulfanilamide (Heintzelman, Hadley and Mellon). Favorable results were also noted by Long [419] in pneumococcic otitis media but not in pneumococcic meningitis, by Mellon and Bambas in a case of brain abscess from pneumococcus type V, and by Hageman in five cases of pneumonia (type unstated) in three of which empyema

occurred. McIntosh, Wilcox and Wright noted a "favorable effect" in one case of type III pneumococcic otitis media, but questionable results in a similar case and in one case of pneumonia (type III) with empyema. [The doses may have been too small; only 0.9 to 1.2 gm. daily.—Ed.] Mitchell and Trachsler noted a favorable effect in a case of type V pneumococcic meningitis in which sulfanilamide (small doses) and optochin were given, but relief was ascribed to the latter drug. Basman and Perley noted favorable effects in a case of type V pneumococcic meningitis, one of type II pneumococcic septicemia, and one of pneumonia (untyped), but no effect in two cases of pneumococcic meningitis and in one of pneumococcic brain abscess (all type III). Whitby found sulfanilamide, proseptasine and soluseptasine ineffective against experimental pneumococcus type I infections, but two new compounds were definitely protective.

[These must be regarded as preliminary studies. In some cases inadequate doses were given, or ineffective blood concentrations attained; in none was pneumococcal arthritis present. Of particular interest is the recent introduction (1938) of alpha-amino-pyridine-sulfanilamide (M and B 693; dagenan*) which is thought to be more effective against pneumococci than is sulfanilamide.]

Syphilis of Joints

Charcot Joints. The features of tabetic Charcot joints described in recent literature were reviewed by Soule. In tabes articular lesions are usually single, and more common in the lower extremities because tabetic cord lesions are generally lumbar. (In syringomyelia joints of upper extremities are more commonly affected due to the high location of the lesion—lower cervical and upper thoracic.) In Soule's case, that of a man aged 47 years with a history of syphilis for 23 years, signs of tabes for 21 years and of tabetic joints for 15 years, unusual features were the multiplicity of lesions (left ankle, right hip, left shoulder), the involvement of areas whose nerve supply is derived from widely separated cord segments, the marked destructive and proliferative articular changes and the marked calcium deposit along fascial planes of foot and leg. Among Lees' 200 cases of tabes were 7 (3.7 per cent) of Charcot joints; in most of the latter signs of tabes were marked but symptoms were few. Tabetic pains or crises were rarely noted in the presence of arthropathy.

Treatment. Antisyphilitic treatment alone will not affect Charcot joints but Lees concluded that considerable recovery from tabetic arthropathy may follow treatment if both chemotherapy and orthopedic measures are used. If affected joints are immobilized early and protected from trauma for some months, effusions may subside, ligaments may become taut, new bone and loose bodies may largely disappear and almost normal articular function may return. [Few reports are as optimistic as this.—Ed.] In later cases the best to be expected is ankylosis in a good position. In advanced cases the surgeon can only attempt to provide support by braces or, if this is impossible, to excise the joint. Sometimes massive bone grafts plus chemotherapy give very good results. Few of Lees' patients required surgical treatment and when used it was not very successful. General treatment

* American name: Sulfanilamide-pyridine (Jr. Am. Med. Assoc., 1938, cxi, 2122).

consisted of tryparsamide intravenously, bismuth intramuscularly; 75 per cent were thus relieved of symptoms.

The fever therapy of early syphilis or early tabes may be an important measure in preventing Charcot joints. *Treponema pallidum* is destroyed in vivo by 5 hours at 39° C. (102.2° F.), 3 hours at 40° C. (104° F.), 2 hours at 41° C. (105.8° F.) or 1 hour at 41.5° C. (106.3° F.) (Boak, Carpenter, Warren 1932). They are made avirulent and immotile in vivo by 1 hour at 42° C. (107.5° F.) or 2 hours at 40° C. (104° F.) (Bessemans and Thiry 1933).

Lees used fever therapy (malaria) in only a few cases resistant to chemotherapy. Marked relief from tabetic pains was usually obtained. Marked clinical and serologic improvement was noted by Epstein in 55 cases of neurosyphilis in which fever and chemotherapy were used. Of five children with congenital syphilis given fever therapy by Spekter and McBryde one was cured, two improved; two given inadequate fever were unimproved. "Distinctly encouraging results" were noted in eight neurosyphilitic patients given fever therapy by Williams. Solomon and Kopp concluded that malaria is not as effective in tabes as in paresis; even after serologic tests become negative, tabetic pains or gastric crises may persist and later Charcot joints may appear. Although they approved of fever therapy they regarded chemotherapy for tabes more highly. Simpson and Kendall summarized their results from fever plus chemotherapy for various types of syphilis: of 15 patients with tabes, eight (53 per cent) were markedly improved, six (40 per cent) moderately improved, one (7 per cent) unimproved.

Brucellosis: Undulant (Malta) Fever

It should be constantly remembered that muscle and joint pains and frank arthritis may be dominant features of brucellosis. Writers are preferring the term "brucellosis" to "undulant fever" or "Malta fever." Although an undulating fever is often the chief feature, the term "undulant fever" is not consistently descriptive, for there is no type of fever pathognomonic of the disease [199]; fever is absent at times, and the term stresses the acute febrile cases to the possible exclusion of the commoner chronic and almost afebrile cases.[295] "Brucellosis" emphasizes the etiology, the Brucella organisms.[27, 413] "Bang's disease" is the animal form of the disease.

Incidence. Although recognized cases are increasing rapidly, chronic brucellosis is still commonly unrecognized (Evans). Gershenfeld and Butts summarized the incidence and mortality rate in various European countries and in the various American States, with data for each year 1928 to 1934, on the relation of human brucellosis to the local prevalence of Bang's disease in each state. Between 1928 and 1934, 9317 cases (8.7 per 100,000 population) with 374 deaths were reported in the United States; the greatest incidence was in Iowa, Kansas, Vermont and Arizona with 37, 28, 26 and 24 cases per 100,000 population respectively. Of 833,185 herds of cattle tested 38 per cent had infected animals; of about 12,000,000 cattle tested, 8 per cent were "reactors" and were found most commonly in Iowa, Kansas, South Dakota and Illinois. The disease is increasing in many states, an increase only partly due to better recognition.

Clinical Data. Thirty papers currently describe the disease as it appeared in almost 700 new cases seen in England,[19, 360, 467, 468, 748] Saskatchewan,[27] South Africa,[96] Arizona,[385] California,[7, 667] Iowa,[741] Kansas,[221] Kentucky,[41] Maryland,[695] Massachusetts,[103, 708] Michigan,[265] Minnesota,[634, 687] New York,[295] North Carolina,[221] Ohio,[456, 749] Oklahoma,[50, 618] Pennsylvania,[220, 337] and Texas.[221]

There are three varieties of *Brucella melitensis:* (1) The melitensis (caprine) strains are limited largely to the goat raising areas of the Southwest; (2) the abortus porcine (or suis) strain, to the hog raising Middle West; (3) the abortus bovine strain is disseminated among cattle widely in the United States (Hardy). All may affect man. The abortus bovine variety rarely affects animals other than cattle and produces mildest infections. Porcine and caprine strains, which also affect cattle, produce more severe disease. In central Pennsylvania, *Brucella abortus* is commoner than *Brucella melitensis.*[337] Evans[222] found the melitensis strains predominant in Charlotte, N. C. and in San Antonio, Tex., less common in Kansas City, Kans. In England *Brucella abortus* prevails (Menton).

Comparing symptoms in 271 cases in California, where bovine strains predominate, to those of Hardy's (1929) 100 cases in Iowa, where porcine strains predominate, Swartout noted certain differences: fever, weakness, sweating, chilliness and headache were commonest symptoms in California; weakness, loss of weight, sweating and anorexia were commonest in Iowa. Joint pains affected 37 per cent of the California, 19 per cent of the Iowa, cases. Symptoms and clinical types of the disease were again reviewed.[103, 199, 221, 413, 741] As noted in previous Reviews the symptoms are protean and the erroneous diagnoses previously made in the cases of Beatty and Harris composed a "staggering list." Characteristic of the disease is the multiplicity of symptoms and the scarcity of physical findings; hence the often repeated dictum, "Think of brucellosis in all cases of prolonged ill defined sickness, in all cases of unexplained fever (especially without localizing signs), in all cases of prolonged disability of the neurasthenic type."[41, 103, 220, 265, 667] Currently stressed were the frequent pulmonary symptoms of brucellosis, often simulating those of tuberculosis.[400, 413, 708] Encephalitis may be produced.[456]

Symptoms Referable to Muscles and Joints. Bovine strains rarely produce articular lesions in man, or in animals inoculated experimentally, but melitensis and porcine strains commonly produce them in animals; in man, porcine strains produce arthritis rather commonly but less often than the melitensis (Hardy). In California arthralgia affected 37 per cent of Swartout's patients; in Iowa it was a prominent complaint of 7 per cent, a minor complaint of 36 per cent, of Hardy's patients. Migratory polyarthralgia most often affected knees, elbows, ankles, shoulders, wrists, fingers and toes, and is commonly misdiagnosed "rheumatic fever" (Swartout). Occasionally joints were red, swollen and painful. One case of massive, relatively painless hydrarthrosis was noted (Hardy). Articular residues rarely occur but suppurative arthritis may affect spines and wrists and re-

semble tuberculosis. Cultures of suppurative lesions are likely to be negative *unless the peculiar cultural requirements for Brucella are anticipated.*

Joints are affected in 25[40] to 40[19] per cent of cases. Arthralgia was common among Woodward's 79 cases; it was present in one of seven acute, and in eight of fifty chronic, cases encountered by Baltzan, and in one of Wainwright's cases. Arthritis was less common, affecting only two of Woodward's 79 patients, one of Wainwright's and one of Casey's patients. According to Dustin, the outstanding symptoms in a third of the cases of chronic, afebrile brucellosis are weakness, and muscle and joint pains. Neuritis and neuralgia are common; severe sciatica has been noted (Avery; Evans[222]). Of special interest was the case of Trueman and Allen:

> A 52 year old farmer removed the placenta of a cow aborting from Bang's disease; the next day dermatitis (erythema brucellum) appeared; two days later the left knee was stiff and swollen but not red or hot. Roentgenograms showed no osseous changes. There was no fever, leukocytosis or constitutional reaction. Agglutinins were present (1:640) for *Brucella abortus* but smears and cultures of the knee fluid, by several methods, were negative. Three months later the knee was still swollen and a hip was painful.

Diagnosis. Confirmation of the diagnosis rests on laboratory procedures, none of which are easy to do or consistently helpful. Their technic, relative value and interpretation were reviewed by several.[27, 50, 103, 220, 223, 265, 266, 332, 467, 468]

Agglutination tests. Some considered these most reliable.[27, 667] "It is vexing to find no accepted standard for a positive test." There is no "diagnostic titer" but strongly positive titers are more significant.[50] Many regard titers of 1:80 or more significant and "positive"; those below 1:80 of little significance. Others, noting proved cases with low titers or negative tests, believe that agglutination tests in any titer should arouse serious suspicions but must of course always be correlated with symptoms and signs.[27, 41, 220, 295] Tests were positive in some dilution in 52 of Beatty's 130 cases; Woodward found agglutinins in 77 of 79 cases (1:80 to 1:2560). Titers gave no index to severity of disease. In all of Swartout's 271 cases agglutinins were present in some (unstated) dilution. [Perhaps this was one of his criteria for diagnosis.—Ed.] Testing 661 patients with fever of unknown origin, the usual causes having been excluded, Campbell and Greenfield found 15 per cent had significant brucellosis agglutinins (1:100 or more in 10 per cent; 1:400 or more in 5 per cent). Gould, Huddleston and their colleagues[850, 851, 858] found agglutinins in only a small percentage of infected patients. During a Detroit epidemic they tested 8124 persons: brucellergin skin tests were positive in 845 (10 per cent); of these 623 were "infected," 222 immune. Only 5 per cent of those infected and 40 per cent of those immune gave "significantly positive tests (1:25 or more)." Of 725 patients with negative brucellergin skin tests, only one possessed significant agglutinins. They regarded agglutination tests as much less reliable than skin tests.

Intradermal test. Others also considered skin tests the most reliable, but these too must be correlated with clinical findings because a positive test may merely represent previous sensitization.[41, 220, 295] Reactions are "negative" unless they remain obvious for 7 to 10 days. Skin tests per se may provoke agglutinins; hence, must not be done prior to agglutination tests.

[Controls should always be used when using skin tests on patients; the antigen is very irritating and often produces a large wheal in normal persons.—Ed.]

Cultures. Blood cultures were positive in only eight of Woodward's 79 cases; in only five of Gould's 845 cases with positive brucellergin reactions. They are difficult to make and take 10 to 30 days to grow: "patients are often well by the time reports are back" (Woodward). Kato and Lane recovered organisms in one case by a new method.

Opsonophagocytic test. This was again described and interpreted.[265, 266, 332] In the hands of the inexperienced it may be as misleading as agglutination tests (Ervin and Hunt). Foshay and Le Blanc considered it valuable in estimating the efficacy of various remedies; they devised a system for interpreting it numerically.

Therapeutic test. This was approved by Beatty. Injections of brucellosis vaccine produce reactions in affected patients but not in others.

Treatment. Because the disease may undergo remission or end spontaneously treatments are hard to evaluate. "Any treatment is good if given at the right time" (i.e., near the finish of a wave of fever) (Woodward).

Chemotherapy. Of 19 patients treated by Woodward with acriflavine, 11 promptly recovered; results were not good, or were doubtful in eight. The patient of Kato and Lane did not respond to prontosil but did to acriflavine. Mercurochrome was of doubtful value.[741] Wainwright noted a rapid favorable effect from neoarsphenamine in six of seven cases, but Kober considered it of no value in one case. The Abbotts recommended the use of metaphen in early acute cases. Some believe that sulfanilamide and related compounds may prove most useful. Diseptal compounds favorably affect experimental Bang's disease (Hoerlein), sulfanilamide is bacteriostatic to *Brucella abortus* (Nitti, Bovet and Depierre 1937), and patients with undulant fever have apparently been benefited by sulfanilamide (Grouès 1936, Thevenet 1936). Prontosil was ineffective in Kato and Lane's case, and in one of Kober's cases. In the first case the dosage was not stated; in the second it was 2 c.c. b.i.d. for two days. Young's patient presumably responded promptly to injections of fouadin, an antimony preparation.

Vaccine. Of 132 patients given *Brucella abortus* vaccine by Harris, 42 per cent were "cured," 36 per cent markedly improved, the rest improved slightly or not at all. Only one of Shuller's four patients responded to vaccine and Beatty considered it only "moderately" successful. The only one of Baltzan's patients relieved by vaccine was one to whom by mistake it was given intravenously instead of subcutaneously; marked fever, shock and rapid improvement resulted. Brucellin, a filtrate of Brucella, was regarded by Gould as the most effective method (no results given). Foshay's antiserum was ineffective in one of Woodward's cases and in that of Casey.

Typhoid vaccine. Intravenous injections of TAB vaccine gave prompt results in two of Kober's cases, in one case of Shuller and in a chronic case of eight years' duration in which Page gave only one injection (100,000,000

organisms). Harris noted no results in two patients so treated. For certain reasons Snell and Magath could not give specific antiserums or fever therapy to a woman 66 years old with acute brucellosis. She was promptly cured by two injections (15,000,000 and 20,000,000 bacteria) with febrile reactions. Dehydration and disturbed electrolyte metabolism accompanied the reactions but were corrected by the use of physiologic solutions of sodium chloride intravenously, suprarenal cortical hormone and salt by mouth. The course of acute and subacute brucellosis was apparently shortened in 10 cases by intravenous injections of mixed typhoid vaccine given by Ervin and Hunt.

Fever therapy. Three sessions of artificial fever (electromagnetic induction) were given by Zeiter to a patient with recurring fever and joint pains for 10 years, and with changes in one hand simulating atrophic arthritis. The fever promptly subsided and the patient greatly improved but some symptoms of arthritis persisted. [Was the arthritis independent of the brucellosis?—Ed.]

Mortality. One of Woodward's 79 patients died of brucellosis. The mortality in the survey of Gershenfeld and Butts was 374 deaths among 9317 cases reported in the United States, 1928 to 1934.

Prophylaxis. Infected milk is the chief but not the sole source of the disease for man. "Mercantile interests are still hammering away at the credulous public to sell it the idea of the superiority of raw over pasteurized milk." The public must be educated to the dangers of raw milk. All milk cows must be tested yearly. The disease can be obliterated but the only hope lies in removing diseased animals from domestic herds.[708, 741]

Typhoidal Arthritis

No cases of typhoidal arthritis were reported. Those who might see such cases should know that although cultures of typhoid and paratyphoid A and B bacilli were unaffected by sulfanilamide in concentration of 1 : 10,000 (Long and Bliss[421]), sulfanilamide apparently had a curative effect on experimental typhoid and paratyphoid B infections in mice (Buttle, Parish, McLeod and Stephenson). Schmidt (1936), using prontosil, noted improvement in three cases of typhoid fever. However, a patient with typhoid fever still under treatment with sulfanilamide (doses unstated) was not being benefited, according to Hageman.

Meningococcic Arthritis

With its parent disease, meningococcic arthritis, which complicates 4 to 7 per cent of cases of meningococcal infection, has been shown to be amenable to treatment by sulfanilamide. Buttle, Gray and Stephenson (1936), Proom and Rosenthal, Bauer and Branham demonstrated the protective action of prontosil against meningococci in mice. Whitby found sulfanilamide and a new compound effective, but proseptasine and soluseptasine ineffective against experimental meningococcal infections. Sulfanila-

mide was successfully used by Schwentker, Gelman and Long in 10 cases of meningococcic meningitis (two with arthritis) and one with septicemia alone. The effect was good in all cases and comparable to that from specific antiserum. The drug was injected intraspinally (total dose of 10 to 30 c.c.) and subcutaneously (100 c.c. for each 40 lbs. body weight) every 12 hours for two days and once daily thereafter until improvement was noted. Krusen and Elkins reported a case of meningococcemia (rash, pains in arms and legs, positive blood culture but no meningitis) in which relief was not given by specific serum; cultures became temporarily negative (for one week) after three sessions of fever (two of 10 hours each and one of 6 hours at 106.5° F.). Prontosil was then given intravenously; the patient promptly recovered although her nasopharynx contained meningococci a year later. Sulfanilamide promptly cured five patients with meningococcus meningitis (without arthritis) seen by Carey, two seen by Basman and Perley and one each seen by Harvey and Janeway and by Brown and Bannick. Some of them had not responded to serum; the spinal fluid of several became sterile within 24 hours after using sulfanilamide. Of two patients so treated by McIntosh, Wilcox and Wright results were favorable in one, "questionable" in one. Three patients of Mitchell and Trachsler rapidly recovered after combined treatment with prontylin orally, 1 per cent sulfanilamide solution (10 to 20 c.c. intraspinally daily), specific serum and antitoxin. A six weeks' old baby with acute suppurative meningococcal arthritis but no meningitis was rapidly cured by Long and Bliss [425] who gave sulfanilamide subcutaneously once (0.6 gm. in 100 c.c. saline) and in milk thereafter for six days.

The combined use of serum and sulfanilamide for meningococcic infections in animals seemed to Branham and Rosenthal to be superior to the use of either alone. The drug alone was more effective when given subcutaneously than orally; a high percentage of treated animals survived fatal doses of bacteria even after only one injection of the drug.

Suppurative (Purulent, Septic) Arthritis

New cases reported were caused by the usual bacteria, *Staphylococcus aureus* and *albus* most often, hemolytic or green-producing streptococci, pneumococci, gonococci and rarer bacteria occasionally. Clinical features of the 69 new cases conformed to those described in previous Reviews.[73, 329, 370, 393, 504, 574] Two points were emphasized: symptoms of suppurative arthritis are much more severe than those of ordinary "infectious arthritis"; patients often dread the slightest motion of bed or bed clothes; in acute monarticular suppurative arthritis juxta-articular osteomyelitis must be suspected. Of 80 patients with acute hematogenous osteomyelitis seen by Robertson, 20 developed adjacent suppurative arthritis: a hip was involved in 11; a knee in 6; ankle, sacro-iliac and elbow joint once each. Hosford reported 12 cases of suppurative arthritis of hips; in six there was adjacent osteomyelitis. Brockway noted eight cases without osteomyelitis

(knee in five, hip in two, ankle once) and 12 cases secondary to osteomyelitis. The case of Oldham was unusual: suppurative arthritis (hemolytic streptococci) of an elbow secondary to an old infected varicose ulcer of a leg; it responded promptly to rest, aspiration and prontosil.

It was again emphasized that roentgenograms are of no value in diagnosis during the first 10 days unless they reveal adjacent osteomyelitis; most important for diagnosis is early aspiration and culture of articular exudate.[329, 370, 393, 574]

Treatment. Prompt, complete evacuation of infective effusions by repeated aspirations and lavage, or if necessary by incision and drainage, is indicated. Traction may be necessary to prevent spontaneous dislocation. Physical therapy and motion are necessary as soon as possible but not until temperatures are normal at least a week. Brockway favored salt pool baths after drainage; his patients without osteomyelitis recovered complete function in from 3 to 5 months, the others took an average of 16 months to recover. Of Hosford's 12 cases recovery was complete in six, with 20 degrees motion in two and ankylosis in four. In Robertson's 20 cases results were excellent in 12, poor in four; four patients died. Although Domagk (1935) and Mellon, Shinn and McBroom noted therapeutic effects of sulfonamide compounds on experimental staphylococcal infections including staphylococcal arthritis, striking results in such human infections have not been noted. Mitchell and Trachsler's patient with staphylococcal septicemia and pyarthrosis was unrelieved by sulfanilamide.

Articular Diseases Due to Hemolytic Streptococci

Certain nonsuppurative or suppurative articular complications may accompany diseases due to hemolytic (or beta) streptococci; e.g., puerperal sepsis, scarlet fever, hemolytic streptococcal osteomyelitis, streptococcic sore throat or otitis media and hemolytic streptococcemia. It is now more important than ever to recognize promptly the bacteriologic identity of these articular complications because of the discovery that sulfanilamide is so effective against certain hemolytic (or beta) streptococci.

Classification of Streptococci. Streptococci were divided by Smith and Brown, 1915, and by Brown, 1919 to 1920, into three main varieties: (1) *Streptococcus viridans* (alpha or green-producing streptococci); these produced in blood broth no hemolysis, on blood agar green pigmented areas around their colonies with areas of partial hemolysis; (2) *Streptococcus hemolyticus* (or beta streptococci); these produced in blood broth hemolysis of erythrocytes, on blood agar zones of clear hemolysis around each colony with *no* intact erythrocytes adjacent to the colonies (beta type of hemolysis or "beta hemolysis"); (3) nonhemolytic (gamma or indifferent) streptococci; these produced no hemolysis or green production either on blood agar or in blood broth. Brown noted another type of streptococcus (alpha prime streptococcus) with characteristics intermediate between alpha (viridans) and beta (hemolytic) streptococci. In blood broth the alpha prime

variety produced no hemolysis, on blood agar it produced slight hemolysis —definite zones of colorless hemolysis, but this type of hemolysis ("alpha prime hemolysis," produced by alpha prime streptococci) could be distinguished from the true type of hemolysis ("beta hemolysis" produced by beta [hemolytic] streptococci) in that microscopic examination showed a more or less dense fringe of nonhemolized erythrocytes next to the alpha prime colony. To this extent then not all hemolytic streptococci are beta streptococci (some hemolytic streptococci being of the alpha prime variety). Sulfanilamide is effective against beta (hemolytic) streptococci but not against alpha or alpha prime (hemolytic) streptococci. Therefore to distinguish clearly which streptococcal infections are being effectively treated with sulfanilamide current writers are speaking not of "beta or hemolytic streptococci" but of "beta hemolytic streptococci" and of "beta hemolysis" (in distinction to alpha prime hemolytic streptococci and "alpha hemolysis").

There are many different groups of each of these three main varieties of streptococci and each of these groups in turn is composed of a number of distinct types. Thus there are many different strains (or types) of hemolytic streptococci: those of scarlet fever, those of erysipelas, those of puerperal fever, etc. Furthermore, bacteriologists speak not only of different strains of hemolytic (or other types of) streptococci but also of different strains of scarlet fever hemolytic streptococci; for example, a bacteriologist studies 50 "strains" of scarlet fever streptococci, meaning the individual strains (all hemolytic) isolated from 50 different cases of scarlet fever.

Lancefield (1933), studying 106 strains of hemolytic streptococci, isolated from a wide variety of diseases and patients in various parts of the world, was able to group practically all of them into five main groups (A, B, C, D, E) differentiated serologically by means of the precipitin reaction, but not differentiable by agglutination reactions. Group A was composed largely of strains of human origin. Group B was obtained from normal cows' milk and from cases of bovine mastitis. Group C was obtained from various lower animals; its members produced equine strangles, endometritis, etc. Group D was isolated from cheese. Group E was found in certified milk. Various strains of *Streptococcus viridans* did not fall into any of these groups. The group-specific substance in the strains of hemolytic streptococci groups A and B (and probably the others also) was identified as a carbohydrate. Thus, Lancefield found a close correlation between the groupings and the animal source.

Later this differentiation was modified and extended by Lancefield and Hare (1935), Plummer (1935) and Hare (1935). It was found that the main reservoir of group A strains was the human nasopharynx. Although the chief source of groups B and C hemolytic streptococci was not human, a few strains of groups B and C hemolytic streptococci were found in normal and sick humans. Four new groups were discovered (F, G, H, K). These groups were occasionally found in humans, generally as nasopharyngeal (occasional vaginal) saprophytes, but rarely caused disease and when they did the disease was slight.

[This was the opinion in 1935.—Ed.]

In summary, to date nine serologic groups (A, B, C, D, E, F, G, H, K) of hemolytic streptococci are recognized but the vast majority of the hemolytic streptococci that cause acute and serious diseases in man belong to group A. Thus, all strains of hemolytic streptococci isolated in scarlet fever and practically all strains from puerperal fever and erysipelas belong

to group A (Plummer 1935). The hemolytic streptococci belonging to the other groups are isolated usually from animals; rarely from man. When present in man, they are found acting mostly as saprophytes; they are only rarely the cause of disease of man and then only of mild disease. [Newer work does not uphold the latter contention; some group B strains fatal to man have been noted.—Ed.]

It is fortunate that most of the hemolytic (or beta) streptococci seriously pathogenic to man belong in group A (Lancefield) because sulfanilamide is effective against this group of hemolytic streptococci. We have already reviewed some of the pioneer work on the effect of sulfanilamide on hemolytic and other streptococci (Domagk 1935, 1936; Tréfouël, Tréfouël, Nitti and Bovet 1935, Hörlein 1936, Colebrook and Kenny 1936, Lavaditi and Vaisman 1936, Buttle, Gray and Stephenson 1936, Colebrook, Buttle and O'Meara 1936, Vermelin and Hartemann 1936). Full details of this work are found particularly in the papers of Long, Long and Bliss, and Bliss and Long and in the new book of Mellon, Gross and Cooper (1938). Briefly, sulfanilamide (in concentrations of 1 : 10,000) and related compounds are markedly effective against group A (hemolytic) streptococci, effective also against groups B and C but ineffective against group D or G [419, 422] (in vitro).

[Recent reports indicate that sulfanilamide is effective in vivo against all beta hemolytic streptococci except groups D and F. Although sulfanilamide inhibits the growth of alpha hemolytic streptococci, gamma streptococci and certain other bacteria in vitro, it is apparently not effective against alpha or gamma streptococcal infections in vivo.—Ed.]

Early foreign reports indicating the beneficial effect of sulfonamide compounds on hemolytic streptococcemia with articular complications were those of Lampert (1935) and Snyers (1936). Foulis and Barr promptly cured a patient with puerperal sepsis and metastatic arthritis as did Scal a patient with hemolytic streptococcemia with metastatic arthritis. With prontosil and sulfanilamide Basman and Perley promptly cured a patient with hemolytic streptococcemia, meningitis and arthritis. In a case of hemolytic streptococcemia with pyogenic arthritis and other complications, and in which Mitchell and Trachsler gave sulfanilamide, the patient rapidly recovered but articular destruction had already occurred.

[In such infections one of us, A. J. K., has noted incomplete relief from sulfanilamide; supplementary surgical treatment may be required.—Ed.]

Arthritis of Scarlet Fever: Postscarlatinal Rheumatism

There are three articular complications of scarlet fever: (1) non-suppurative scarlatinal arthritis with sterile exudates, (2) suppurative scarlatinal arthritis with hemolytic streptococci in purulent exudates and (3) scarlatinal or postscarlatinal rheumatism—an acute form of polyarthritis representing latent rheumatic fever activated by scarlatinal streptococci.

The incidence of scarlatinal arthritis (types 1 and 2) was 99 cases (1.8 per cent) among 5549 patients with scarlet fever seen by Boyd between 1933 and 1936. Excluding 1936, when convalescent serum was often used, the incidence was 85 (2 per cent) among 4077 cases, an incidence lower than that previously cited, probably because of the recent mildness of the disease.

Type 1. In Boyd's series, nonsuppurative scarlatinal arthritis affected females (70 patients) oftener than males (29 patients); older children and adults oftener than young children. It may occur any time in the course of the disease, but usually between the fourth and tenth days, and generally it affects a few small joints symmetrically, often in rotation. Generally subsiding in two to five days, it may recur briefly a week later. Symptoms are increased fever, stiffness, fairly severe pain, slight tenderness, swelling from effusion and periarticular involvement. Some would classify this type with type 3 as also a manifestation of rheumatic fever (e.g., Paul, Salinger and Zuger, 1934). But Boyd considers it a toxic form of arthritis unrelated to rheumatic fever because not a single case was complicated by endocarditis. Treatment included methyl salicylates externally and salicylates orally; of the latter, 5 grains to young children, 10 grains to older children, 20 grains to adults every 3 to 4 hours. When not tolerated orally, salicylates can be given morning and evening by rectum, half the daily dose in 4 ounces of starch paste.

Type 2. Suppurative arthritis was rare in Boyd's series: three cases among 5549 patients. The three patients were seriously ill with hemolytic streptococcemia. Affected were a knee in one case, a knee and wrist in one, a finger in the third. Joints were painful, swollen, red, hot and tender. The patients recovered under treatment by scarlet fever antitoxin, convalescent serum, sulfanilamide, repeated transfusions, and incision and drainage of joints.

Type 3. Many patients with inactive rheumatic fever escape exacerbations thereof during scarlet fever but Boyd noted two who did not. Rheumatic fever may be precipitated during or just after scarlet fever; its exact relationship thereto is not fully understood.

Arthralgia affected 3 per cent of young adults being immunized against scarlet fever by Healey. Generally appearing within 12 hours after a dose of scarlatinal streptococcus toxin the arthralgia, with or without swelling, lasted a few hours to several days, disappearing without residue. To determine the cause of these joint pains Healey gave to different groups of 63 patients: (a) unheated toxin in broth media, (b) the toxin heated to destroy the soluble toxin and (c) diluted broth media containing no toxin. Arthralgia was produced only by the toxin in 75 per cent of cases, chiefly but not solely by the toxin in 17 per cent, by proteins of broth and not by the toxin in 8 per cent. Since 84 per cent of these 63 patients had previously had arthralgia or rheumatic symptoms suggestive of streptococcal infection, Healey concluded that patients, so affected previously, are sus-

ceptible to subsequent provocation of arthralgia by unrelated toxins including the scarlatinal.

Treatment with Sulfanilamide. Definite conclusions on the value of sulfanilamide in scarlet fever cannot be drawn from the earlier work; details were scanty and dosage often low (Püschel 1935, Scheurer 1936, Maraun 1936). Recent results have been more definite. Peters and Havard treated 150 patients with "proseptasine" and 150 patients otherwise. The average duration of fever was greater in the sulfonamide-treated group than in the control cases but none of the former patients died, against two in the control group. Complications affected only 35 per cent of the drug-treated group, 56 per cent of the controls. In particular, invasive phenomena: e.g., endocarditis, rheumatism, were distinctly less common among those receiving sulfonamide: "Rheumatism" affected only 2 per cent of those treated with sulfonamide; 6.6 per cent of the others. Other writers,[421, 422, 530] without referring to scarlatinal arthritis, noted favorable results. In Hageman's eight cases the toxic phase was unaffected by sulfanilamide but no complications arose. The results of others have been less definite.[38, 459]

Rheumatic Fever

Incidence. Many new statistics were reported on the incidence and clinical manifestations of rheumatic fever and rheumatic carditis in various parts of the United States, England, Australia, New South Wales, China, Malaya (Dicum), and the Punjab. Among 33,297 Philadelphia school children (11 per cent of the total) Cahan found 159 with suspected and 191 with definite carditis; of the latter, in 129 the condition was rheumatic and in 18 "probably rheumatic." Although rheumatic fever is common in London, Cove-Smith stated that "flagrantly acute cases" are becoming increasingly rare; responsible factors were a gradual attenuation in virulence during the last 20 years, higher standards of living, improved nutrition, and the prophylactic work of the London County Council. Rheumatic carditis is much commoner in Bristol, England (1.9 cases per 1000 total population; 7.7 per 1000 school population) than in nearby cities; for example, the rate in Bath was only 0.2 per 1000 total population, 1.3 per 1000 school population (Perry and Roberts). Wallace found the disease definitely increasing in Edinburgh; a hospital incidence of 5.6 per cent of the total medical admissions was noted in 1934. In the state of Victoria, Australia (population 1,852,171) there are yearly about 1303 new cases of rheumatism (rheumatic fever, chorea, or carditis), a rate of 0.7 per cent, and 1 per cent of the population have cardiac rheumatism (Graham). In New South Wales the incidence of rheumatic carditis (0.3 to 0.6 per cent in different hospitals), was much less than that in Europe or the northern United States but much greater than that in the tropics (Maddox). Among 62,991 country school children in New South Wales, 2.7 per cent had "rheumatism" and 0.6 per cent had rheumatic valvulitis. In north

China the incidence of rheumatic fever and chorea is higher (0.57 per cent of all medical admissions) than previously reported but considerably less than that in European and northern American cities (Chang and Dieuaide); it approximated that of St. Louis.

Predisposing Factors. 1. Geography and climate. Further evidence was presented to show that the disease is more prevalent in the North than in the South. Paul and Dixon examined American Indian school children on reservations in Montana and Wyoming, northern New Mexico and northern Arizona and in southern Arizona. Definite rheumatic carditis was found in 31 of 688 children (4.5 per cent) in the two northern regions; in 21 of 1106 (1.9 per cent) in the two central regions; in only 5 of 1019 (0.5 per cent) children in the southern group. Thus, the disease was almost 10 times more frequent in the North than the South. Significance was attached to its frequent occurrence in the cold but dry climate of Montana and Wyoming where it was twice as frequent as it is in New England (2.2 per cent incidence). Sharp and John compared the incidence in Chicago and in Galveston, Texas. The incidence of rheumatic carditis without arthritis was 0.35 per cent of hospital admissions in Chicago, 0.08 per cent of those in Galveston. "Acute rheumatic affections" were about six times more frequent in the North. Acute rheumatic fever without chorea or carditis occurred about four times, chorea about 33 times more often in the north. However, old rheumatic carditis occurred almost as often in Galveston as in Chicago. Hence, the southern climate apparently affords its residents much more protection against chorea than against other rheumatic affections, and diminishes the severity more than it does the incidence of rheumatic fever. Seasonal variations in the incidence of throat infections with hemolytic streptococci were noted and somewhat paralleled those of rheumatic attacks but not sufficiently to consider the throat infections the chief factors in the rheumatic attacks. In New South Wales the distribution of "rheumatism" * was fairly even over the country but rheumatic carditis was more frequent on tablelands and slopes than in coastal regions (Maddox).

Kamra emphasized that rheumatic fever does exist in the Punjab. Of 1000 patients examined, two had "acute articular rheumatism," six had rheumatic endocarditis. In one village the incidence of rheumatic fever was 2.13 per 1000 of the total population, an incidence comparable to that in England.

2. Season. Only 13 per cent of the Galveston cases occurred between June and September; in Chicago the summer reduction was not nearly so striking (Sharp and John). Among the 141 Chinese cases of Chang and Dieuaide, 39 per cent of attacks came in winter (Dec.–Feb.), 35 per cent in spring (Mar.–Apr.); an abrupt rise occurred in December, a rapid fall in June. The seasonal curve differs from that of New York in its wider

* In this section on rheumatic fever it is to be understood that "rheumatism" and "acute rheumatism" mean "rheumatic fever" or "the rheumatic state."

range from winter to summer, and from that of Glasgow in the absence of any autumnal rise. The distribution in Peiping was somewhat similar to that of San Francisco. In Sydney, Maddox noted no definite seasonal incidence among hospitalized patients.

3. Social and hygienic factors. Contiguity was an important factor in the incidence of rheumatic carditis. In Dewsbury, England, most patients were from the most congested part of town (Elder). In Bristol there was a "large and highly significant association" between the incidence of the disease and the density of school children per room in the various city wards (Perry and Roberts). In Sydney, Australia, most of the patients were from the poorer industrial quarters of the city, very few from the better class suburbs.

4. Family and heredity. The incidence of rheumatic fever or carditis in families of nonrheumatic children was only 5 per cent (Wallace); that in families of rheumatic children was 23 per cent in Cahan's series, 30 per cent in Wallace's series, but only 11 per cent in Maddox's cases and only 8 per cent in those of Chang and Dieuaide. The latter consider such data generally unreliable. The previously reported familial incidence has ranged from 15 to 58 per cent. Three factors have been held responsible; (1) a common environment, (2) communicability, (3) susceptibility, probably on an hereditary basis, resulting from a familial weakness of tissues of mesenchymal origin, a familial lack of natural protection against the disease. Connor accepted the latter explanation. As a result of a thorough study of 112 rheumatic families [which study deserves more attention than we can give it here.—Ed.] Wilson and Schweitzer concluded that an hereditary factor, transmitted as a single autosomal recessive gene, is distributed among the population, which makes the bearer susceptible to rheumatic fever. The exact rôle of environment and contagion could not be determined. Hereditary susceptibility seemed to determine the familial incidence of rheumatic fever but it may not necessarily be the sole condition essential for its development.

Wilson and Schweitzer studied 112 rheumatic families comprising 468 rheumatic children aged three years or more; the families were observed for an average of nine years. Although unfavorable environment increased the incidence it was not responsible for the observed familial incidence. Nor was communicability found to be the chief factor. More important was the hereditary factor. Of the 112 families, in 50 per cent (55 families) one or both parents were rheumatic; in the remaining 57 families neither parent was rheumatic, but in 46 per cent of these 57 families there were rheumatic persons on the maternal or paternal side. Thus, in only 28 per cent of the entire 112 families was there no family history of rheumatism. Of four sets of identical twins all were alike in having rheumatic fever; of 12 pairs of fraternal twins, five had similar experiences (i.e., both were either affected or were free) and seven were dissimilar in experience. The hereditary mechanism involved a single autosomal recessive gene. Dominance involving one or more genes, recessives involving two or more genes, and sex linkage were all excluded.

[Such a study on the heredity of atrophic and of hypertrophic arthritis would be very valuable.—Ed.]

5. Sex. Among 750 juvenile patients with rheumatic fever studied in New York by Roth, Lingg and Whittemore, 54 per cent were females; among 488 patients with rheumatic carditis 51 per cent were females. In Australia, of 382 rheumatic rural children 51 per cent were females, of 428 urban children, 47 per cent were girls.[435] Of 141 Chinese patients (including adults) with rheumatic fever, 38 per cent were females.[107]

6. Age. The patients of Chang and Dieuaide included adults. The disease appeared before the age of 30 years in 82 per cent, most often at the age of 14 years. In Australia children hospitalized for rheumatic fever were most frequently nine years old at the onset of their disease. Among the 488 cases of juvenile rheumatic carditis reported by Roth, Lingg and Whittemore the mean age at onset was eight years; the mode seven years. A fourth of initial affections occurred in preschool ages. The mode age of onset varied with the manner in which the disease first appeared: in polyarthritis it appeared about the age of five; in carditis, about six; in chorea, between seven and eight years of age. Leonard confirmed the observation of others that the factor of age is important and that if a child escapes acute rheumatism prior to puberty (age 13 to 15) he is likely to escape it entirely or be affected much less severely. Leonard studied 500 children with rheumatic fever; 71 per cent developed carditis. The initial attack generally came between the ages of 5 and 11 years. He observed 100 patients for several years; all had at least one recurrence; 60 per cent had two. At or about puberty there was a sharp decline in the incidence of both initial attacks and recurrences.

General Symptomatology. "Nervousness" has been considered characteristic of rheumatic or "prerheumatic" children. Neustatter could not confirm this impression: rheumatic children are more nervous than normals but no more so than those with other illnesses; rheumatism may aggravate a child's tendency to nervousness but does not cause it. The "typical rheumatic child" was again described.[13] Among the 488 cases of juvenile carditis seen by Roth, Lingg and Whittemore initial symptoms were: polyarthritis alone in 45 per cent, with carditis in 16 per cent, with chorea in 4 per cent, with chorea and carditis in 1 per cent (i.e., polyarthritis in a total of 66 per cent); carditis alone in 14 per cent, with chorea in 1 per cent; chorea alone in 19 per cent. Polyarthritis was the most common initial sign among both girls and boys; as an initial manifestation chorea, with or without carditis, affected girls more often than boys.

Among Maddox's 428 cases of juvenile acute rheumatic fever, early symptoms were arthralgia in 97 per cent, arthritis in 28 per cent, sore throat in 23 per cent, vomiting in 9 per cent, abdominal pain in 8 per cent, cough or cold in 8 per cent, stiff neck in 3 per cent, choreiform motions in 1.5 per cent; rashes, generally morbilliform, in 14 per cent, pyelitis in 2 per cent, nodules (rare in Sydney) in only 1.5 per cent. [This low incidence of nodules is not satisfactorily explained.—Ed.] Carditis affected 59 per cent of the total: 46 per cent of 308 in their first attack, 64 per cent of 120 in their second attack. In those so affected endocarditis appeared with great rapidity. Pericarditis was present in 2 per cent of 396 nonfatal cases, in 13 per cent

of 32 fatal cases. Only 16 per cent of the 428 patients had valvulitis without previous febrile rheumatism or chorea. In Sydney therefore the clinical features differ little from those noted elsewhere except for the absence of a seasonal incidence and the rarity of nodules.

The clinical features in the 141 Peiping cases, adults and children (Chang and Dieuaide) were carefully analyzed: present were fever in 97 per cent, polyarthritis in 92 per cent, leukocytosis in 83 per cent, carditis in 64 per cent, anemia in 60 per cent, headache in 28 per cent, congestive failure in 22 per cent, nausea in 20 per cent, precordial pain in 19 per cent, skin lesions in 17 per cent, vomiting in 16 per cent, nodules in 15 per cent, pleurisy in 13 per cent, epistaxis in 13 per cent, pericarditis in 12 per cent, hematuria in 11 per cent, abdominal pain in 11 per cent, chorea in 9 per cent and bronchopneumonia in 4 per cent. Also reported were the incidence of polyarthritis, carditis and chorea alone and in combination, the various joints affected, types and combination of cardiac lesions, site of nodules, etc.

Among 73 rheumatic patients seen by Massell and Jones the following appeared: fever in 53 per cent, nodules in 41 per cent, chorea in 29 per cent, epistaxis in 25 per cent, joint pains in 23 per cent, rash in 19 per cent, precordial pain in 19 per cent, congestive failure in 18 per cent, abdominal pain in 14 per cent, pneumonia in 10 per cent, pericarditis in 7 per cent and pleurisy in 4 per cent.

The first symptom of rheumatic fever among Wallace's 516 juvenile cases in Edinburgh was chorea in 44 per cent, arthritis in 37 per cent, "primary carditis" in 19 per cent. During the first attack carditis developed in 53 per cent.

Special Clinicopathologic Data. 1. Heart. The clinical and statistical data on rheumatic carditis in current literature are too voluminous to be summarized here. For details reference must be made to the original reports.[13, 93, 107, 306, 387, 435, 587] They emphasize again the tragic and enormous morbidity and mortality from rheumatic carditis. Rheumatic carditis should be regarded as the chief manifestation, not a complication, of rheumatic fever.[306] In 1930, when the population of the United States was about 122,000,000, there were about 840,000 cases of rheumatic carditis in the country (Paul 1930); now with a population of about 130,000,000, it has been estimated that there are over 1,000,000 Americans with rheumatic carditis (Hedley). In Canada there are 25,000 school children with rheumatic carditis, 3000 in Montreal alone (Cushing). A child 10 years old is three times as likely to die from carditis as from any other disease. Rheumatic fever is responsible for from 15 to 40 per cent of carditis at all ages, and for 90 per cent of all juvenile carditis in the United States. Rheumatic carditis annually causes 40,000 deaths in the United States, the average age at death being 30 years (Hedley). In Dewsbury, England, 70 per cent of juvenile carditis was rheumatic (Elder). Observing 337 patients with rheumatic fever over a period of 20 years Wilson found the heart practically always (eventually) affected. Even in early attacks only about one patient in every four escapes carditis, but patients with chorea seem to develop carditis less frequently (Warner). Warner emphasized an "extraordinary fact": If a child survives two attacks of chorea without developing carditis he never seems to develop carditis in future attacks of chorea. In cases of juvenile rheumatism, carditis and polyarthritis were so frequently associated, and patients thus affected thereafter

ran so true to type as to suggest to Roth, Lingg and Whittemore that they represent a similar method of response. Many patients (25 to 50 per cent) with juvenile rheumatic carditis give no history of fever, acute polyarthritis or chorea; this was so in 50 per cent of 43 cases of rheumatic carditis seen by Sherwood at necropsy.

A basal pericarditis appeared to Wolffe and Digilio to be the earliest manifestation of low grade juvenile rheumatism; it produced in the left second and third costosternal junctions, occasionally at the apex, a somewhat musical friction-like murmur, generally systolic, occasionally diastolic, sometimes transitory and often misinterpreted as due to mitral or aortic valvulitis or pulmonary arteritis.

The significance of cardiac murmurs has been overstressed, that of heart tones understressed: from the intensity of the first heart sound Keith believed he was able to predict the length of P–R intervals with fair accuracy. An accentuated first sound is more diagnostic of mitral stenosis than the middiastolic murmur. Heart valves are relatively immune to damage from rheumatic fever in adult life for reasons not yet clear. Kugel and Gross (1921, 1926) confirmed Langer's finding (1880) that fetal valves possess blood vessels but most adult valves do not; it was concluded that when valvular vessels do not regress but remain patent in adults they render the patient liable to embolic valvulitis. This explanation is unsatisfactory to some. Gross now believes that only very rarely do normal valves possess blood vessels; vascularity even in normal-appearing valves is almost always the result, not the cause, of antecedent rheumatic inflammation. According to Wearn and Moritz, however, 84 per cent of normal heart valves possess blood vessels; active or healed valvulitis can be found in the absence of blood vessels, and the incidence of blood vessels in a given valve does not correspond to the incidence of rheumatic valvulitis in that valve. Conner concluded that differences in the reactions of juvenile and adult valves to rheumatic fever depend not on the vascularity of a valve but on differences in the disease itself in the two age groups.

Uncomplicated aortic insufficiency is extremely benign (Conner). Patients so afflicted are able to pursue lives normal in activity and length and die ultimately of some other disease unless they develop (as they sometimes do) subacute bacterial endocarditis. Patients with aortic stenosis, once failure supervenes, die quickly; this was again noted by Thompson and Levine who, however, noted the paradox that although patients with tricuspid stenosis may die early, they are able to tolerate their symptoms considerably longer than those whose tricuspid valves are not affected. Auricular thrombi may result from severe mitral stenosis, congestive heart failure and auricular fibrillation. Appropriate stains will distinguish the fibrin material in thrombi from the focal swelling of collagen (fibrinoid swelling of Klinge) in the same tissue (Graef, Berger, Bunim and Chapelle). Rae noted a case of presumed leukemia (leukocytes 76,000) proved at necropsy to be one of acute rheumatic fever with coronary aneurysms

and thrombosis with infarction, the leukocytosis being a response to the thrombosis. Other reports of interest were on the effect of rheumatic carditis on the superior vena cava (Waaler), on the development of experimental endocarditis with an extensive review of literature (Nedzel), and a critical historical appreciation by Keil of the work of Wells (1812) who first described rheumatic nodules and was one of the first to emphasize the relationship of carditis to rheumatic fever.

2. Joints. Fisher examined synovial membrane from a sternoclavicular joint of a young girl dead after four weeks of rheumatic fever. Present were many of the specific pathologic reactions seen in rheumatic hearts: areas of fibrinoid degeneration in synovial villi and membrane and in the subintima of blood vessels; vascular endothelial proliferation and perivascular cellular reactions resembling Aschoff bodies. According to Fisher, areas of fibrinoid degeneration (first described by Neumann 1880, 1896, recently by Klinge, 1932) are not specific for rheumatic fever but are also seen in synovial membranes in atrophic arthritis.

3. Muscles. It is important to distinguish fatigue pains or nonrheumatic "growing pains" of children from "true rheumatic growing pains"; the latter occurred early in many of Wallace's rheumatic children. All children have muscle pains on occasion (present in 13 per cent of 600 nonrheumatic children) but Wallace regarded as significant pains severe enough to keep children from school two to three days. Normal growth does not cause pain. Muscle pains due to fatigue or poor posture generally affect lower extremities and appear after exercise or at the end of the day. Rheumatic pains generally affect upper extremities also, are not especially related to exercise and appear any time of day although especially at night (Rothbart).

4. Nodules. These were present in 15 per cent of the 141 cases of Chang and Dieuaide. The histopathology of subcutaneous nodules in rheumatic fever was carefully described by Mote, Massell and Jones, and by Collins. It was compared to that of induced nodules in rheumatic fever, spontaneous nodules in atrophic arthritis and those from trauma in nonrheumatic patients.

The sequence of events in the evolution and regression of rheumatic nodules was (Mote, Massell, Jones): a structural alteration in collagen, resulting edema and deposition of fibrin-like material; concurrently or shortly thereafter vascular damage and polymorphonuclear leukocytic and lymphocytic infiltration, with proliferation of primitive perivascular mesenchymal and other cells which invade the borders of the altered collagen foci; subsequent gradual organization progressing from perivascular areas toward the centers of the necrotic foci; concurrently a typical cell reaction—closely packed, radially arranged, basophilic mononuclear and multinuclear cells which stain somewhat like fibroblasts and which can deposit intercellular collagen. The outcome is a progressive organization to normal replacement of the lesion with fibrous tissue.

Subcutaneous nodules were induced by Massell, Mote and Jones by injecting 2 to 3 c.c. of the rheumatic patient's own blood into the olecranon

region; in some cases, friction was applied daily thereto. Regardless of this, 45 per cent of 82 rheumatic patients developed induced subcutaneous nodules essentially similar to the spontaneous type. Only one of 34 non-rheumatic persons so treated developed nodules.

[Similar experiments should be made on patients with atrophic arthritis, hypertrophic arthritis and even gouty arthritis.—Ed.]

A discussion of the comparative pathology of the nodules of rheumatic fever and of atrophic arthritis will be given later.

5. Lungs and pleura. Gouley again described " rheumatic pneumonia " and pneumonitis, the latter being a lesser degree of lung involvement without consolidation. Often seen, they are part of rheumatic fever, not complications, but are often overlooked as they are transient. Signs are more striking than symptoms. An occasional complication is basal pulmonary atelectasis or " inflammatory collapse," which may be the basis for Ewart's sign. Due to the interstitial fibrosis that follows rheumatic pneumonitis, lungs may never return to normal. The resultant respiratory insufficiency is probably a factor in the right ventricular failure heretofore blamed entirely on mitral stenosis.

In the Peiping series,[107] pneumonia affected 3.5 per cent, and pleurisy affected 13 per cent of the 141 patients. The incidence of rheumatic pleurisy has been given as from 3 to 10 per cent. It affected only two of Gouley's 25 patients with rheumatic pneumonia who came to necropsy. In Edstrom's group of 850 patients with rheumatic fever pleurisy affected 4.5 per cent. The clinical and differential diagnosis were discussed; also the necropsy findings in 36 cases.

6. Skin and mucosa. Erythema marginatum occurs in from 4 to 15 per cent of rheumatic children and is " specific " for rheumatic fever. It was again described.[435, 540] It usually appears first with an initial attack or a relapse. It may be transitory but may continue long after all other signs of rheumatism have disappeared. Since all cardiac abnormalities in 4 of 13 patients so affected disappeared Perry regarded the erythema as of good prognostic import. [The series of cases seems too small for one to draw definite conclusions.—Ed.]

According to Brim, one may find rheumatic nodules not only in skin but also smaller nodules in the oral and pharyngeal mucosa of many rheumatic patients. These nodules, " a new sign " of active rheumatic fever, varied in size " from pin-point to pin-head " and formed smooth, pink (or white capped), round elevations on the mucosa especially of the anterior faucial pillars and on contiguous tissues. They may occur with or precede other rheumatic manifestations. Their presence was not seasonal but was related to the rheumatic activity.

Laboratory Data. 1. Electrocardiograms. The electrocardiographic alterations seen among 100 children who had rheumatic carditis were described in detail and compared with those in 50 cases of congenital heart disease (Drawe, Hafkesbring and Ashman). In general, electrocardio-

grams merely confirm the evidence of rheumatic activity provided by leukocyte counts and sedimentation tests but Massell and Jones noted occasional cases in which long P–R intervals were the only signs of active rheumatism. Fourth lead electrocardiograms have not yet been finally evaluated. In rheumatic children Messeloff and Pomerantz found that Lead IV gave no more data than the three standard leads. Dwan and Shapiro found fourth lead electrocardiograms of no value in cases of congenital heart disease but in cases of rheumatic carditis they amplified and corroborated data from other leads so that myocarditis was diagnosed in 29 per cent of cases by orthodox leads, in 7 per cent more by Lead IV.

2. Sedimentation rates. Studying 163 rheumatic subjects, Massell and Jones noted the comparative value of the sedimentation test and the leukocyte count as indices of rheumatic activity. These tests were helpful, often essential in determining mild activity. In most cases, results of one or both of these tests continued at an elevated level for several weeks to many months after the disease was clinically inactive. In detecting low-grade activity the tests were of equal value but the corrected sedimentation index was the more useful because of inherent errors in making leukocyte counts. Results of one or both tests may be normal in the presence of active rheumatism. In 58 of 163 cases the sedimentation rate remained elevated longer than the leukocyte count; in 55 the reverse was true; in 50 cases both tests became normal simultaneously. Rates may become elevated [but not always.—Ed.] and remain elevated for as long as three weeks after upper respiratory infections or tonsillectomy; hence, elevated rates within three weeks of these events do not necessarily indicate active rheumatism. In conclusion, continued leukocytosis or repeatedly rapid corrected sedimentation indices should, in rheumatic patients, be considered indicative of active subclinical disease in the absence of other cause for their abnormality.

3. Blood counts. An arbitrary level of 10,000 leukocytes per cu. mm. was considered the upper limit of normal by Massell and Jones; in the convalescent stage of rheumatic fever counts were usually not over 12,000 to 14,000. Rae's interesting case of rheumatic fever with leukocytosis (76,000) due to coronary thrombosis was noted. Gwynn reported a case of macrocytic anemia due to fatal, fulminating rheumatic fever.

Relationship of Rheumatic Fever to Other Diseases. 1. To congenital heart disease. Evans found no relationship between acute rheumatism of mothers before or during pregnancy, or of fathers, and the congenital heart disease of 30 children.

2. To subacute bacterial endocarditis. Gross and Fried studied the hearts in 70 cases of acute or subacute bacterial endocarditis. Previous rheumatism had affected 75 per cent of them; certain histologic stigmata indicated those cases in which bacterial endocarditis was superimposed on rheumatic carditis. Rheumatic activity was not a necessary precursor of bacterial endocarditis. Aschoff bodies were found in about 30 per cent of the cases of superimposed endocarditis but in some cases the rheumatism

was reactivated by the superimposed bacterial endocarditis rather than vice versa. Eosinophilic necrosis of valve closure lines seemed to predispose to bacterial implantation. Since this is seen more often in acute rheumatism, rheumatic hearts are more susceptible to bacterial endocarditis. Vascularization of valves played no significant rôle. Kinsella noted points of similarity in the pathology of *late* rheumatic valvulitis and of bacterial endocarditis but the *earliest* cellular reactions of rheumatic valvulitis were distinctive; hence, bacterial endocarditis is not an inherent part of rheumatic valvulitis.

3. To chorea. This will be discussed under the heading "chorea."

4. To atrophic arthritis. This will be discussed under "atrophic arthritis."

5. To erythema nodosum. According to Keil, there are four theories concerning the etiology of erythema nodosum: that it is (*a*) a specific disease; this is the attitude of many dermatologists; (*b*) tuberculous; this is held by many pediatricians; (*c*) rheumatic, probably streptococcal; this is the view of many internists; (*d*) a nonspecific toxic reaction to different causes. Keil summarized the evidence for and against its rheumatic origin. In favor of a close relationship of the two were the fact that it is often associated with sore throat and joint pains. Facts which do not support a relationship are as follows: there is no "true rheumatic throat"; many nonrheumatic infections are accompanied by sore throats; the joint effusions and severe degrees of pain seen in rheumatic fever rarely occur in erythema nodosum; in erythema nodosum carditis, significant electrocardiographic changes, chorea, subcutaneous nodules and pleurisy practically never occur, and salicylates are of no curative value; finally the skin reaction in erythema nodosum is clinically different from that ever seen in true rheumatic fever. Therefore there is no sound evidence that erythema nodosum is rheumatic: "It will not do to label cases of erythema nodosum as tuberculous when the tuberculin test is positive, and as rheumatic when the test is negative."

Erythema nodosum is a nonspecific reaction of skin to a variety of bacterial, toxic or chemical agents; so concluded Spink after a survey of 143 cases and a review of the literature. In Spink's cases the highest incidence was among females 20 to 29 years of age. The disease may accompany tuberculosis (especially in children), hemolytic streptococcal infections and rheumatic fever; lesions similar to it were produced by injections of tuberculin, or of streptococcal nucleoprotein, autogenous or otherwise. To Spink a relationship to streptococcal infections was more evident than one to tuberculosis.

Differential Diagnosis. Rheumatic fever is one of the most protean of all diseases; hence, it is unfortunate that there is no clinical sign or laboratory test pathognomonic of the disease.[174, 557] Some of the difficulties of distinguishing it from gonorrheal or acute atrophic arthritis were illustrated (Wainwright and Janeway).

Course, Prognosis, End Results. Emphasizing the chronicity of the disease, Sherwood warned that in an acute attack one should expect the fever to last for days, tachycardia and leukocytosis for weeks, the altered sedimentation rates and electrocardiograms for 2 to 12 months, anemia and loss of weight for four months and more. Current data again demonstrated the great tendency to recurrences. Of the 488 rheumatic children studied by Roth, Lingg, and Whittemore, 68 per cent had at least one recurrence during the observation period of 8 years, 40 per cent had two or more; some had three to five; a few had six or more; of the recurrences, 73 per cent appeared within three years of the initial attack. Recurrences affected those who first developed carditis or chorea more often than those first affected by polyarthritis alone or with carditis. Relapses within one year affected 18 per cent of the 141 Chinese cases [107]; over 10 years elapsed between recurrences in 11 cases. Wilson also noted long (7 years) spontaneous remissions, a point to remember in evaluating any treatment. Recurrences were much less frequent among those who had attained puberty (13 per cent affected) than among those who had not (66 per cent affected).

Factors related to pregnancy which tend to precipitate cardiac failure among rheumatic women were: increases in body weight, blood volume and basal metabolic rate; the high diaphragmatic position which lessens pulmonary volume and excursion and distorts heart and great vessels, and the care of the child after birth (Hepburn). Indications for permitting or terminating pregnancy among rheumatic women were detailed. Various factors must be considered, not only the apparent functional cardiac ability, and each case must be decided individually. Among 5366 pregnant women Lamb found organic heart disease in 110 (2.1 per cent); in 102 of them, of rheumatic origin. Heart failure during pregnancy affected more than 50 per cent of those with active rheumatism.

Of 337 patients, 112 (33 per cent) died during Wilson's 20 year period of observation. Carditis practically always developed; in 85 per cent of them before the age of 17 years; the average age at death was 12.6 years. Aside from active carditis the type of rheumatic manifestation first noted carried no prognostic significance. Wallace stated: "It is a solemn thought that 25 per cent of all rheumatic children die from heart disease before they leave school and a further 30 per cent are crippled for life."

Etiology and Pathogenesis. No new theories or important variations of old theories were entertained.

Factor of infection. 1. Upper respiratory tract infection. The exact rôle of tonsillar or pharyngeal infections remains uncertain. Among Maddox's 428 hospitalized rheumatic children 102 had sore throats one or two weeks prior to the onset of their acute rheumatism, but in the country sore throats were as frequent among nonrheumatic as among rheumatic children. Sharp and John attempted to determine the significance of the lowered incidence of rheumatic fever and of hemolytic streptococcal sore throats in Galveston, as compared to Chicago. A definite seasonal drop in strepto-

coccal carriage in throats was noted and was lowest in warm weather. Hemolytic streptococci were present in 42 per cent of 908 throat cultures made between October and May, in only 13 per cent of 251 cultures made between June and September. The southern climate reduces, but does not eradicate, tonsillitis. However, throats became sterile of streptococci irrespective of season, and Sharp and John could not conclude that a reduction in oral streptococci was the agency by which southern climate controls the disease. Although the seasonal decline of rheumatic fever and streptococcal throats in Galveston coincided, the incidence of rheumatic fever and especially of chorea continues to remain low throughout the year and does not parallel the winter rise in pharyngeal infections.

The hemolytic streptococci isolated by Keefer and Spink in cases of tonsillitis preceding rheumatic fever were apparently similar biologically and serologically to those in cases of erysipelas and other human hemolytic streptococcal infections. Yet rheumatic fever did not follow erysipelas once in more than 1400 cases of the latter.

In New York, however, the relation between streptococcal pharyngitis and acute rheumatism seemed distinct to Bradley, who studied 550 persons including patients with active, convalescent, and quiescent rheumatism. At some time, 20 per cent of them carried hemolytic streptococci, usually potentially pathogenic to man, of distinct serologic types which varied from time to time. Family epidemics were caused by a single (but variable) type. Of 14 rheumatic patients affected by hemolytic streptococcal pharyngitis 43 per cent had relapses but none of 31 rheumatic patients who escaped streptococcal pharyngitis and none of nine who developed nonstreptococcal pharyngitis had relapses. "There is nothing haphazard about streptococcal infections." According to Bradley an apparently sporadic case of rheumatic fever is not an isolated event but almost certainly part of a streptococcal epidemic of distinct type. Every case of "tonsillitis" should be considered, not a possible example of chronic endogenous infection, but as a dangerous manifestation of an acute exogenous infection—"epidemic streptococcal fever."

2. Skin tests. To determine whether skin tests might serve to identify causal organisms in rheumatic patients, Traut tested the skin in seven cases of rheumatic fever, six of old rheumatic carditis, nine of "rheumatic pains," 20 of atrophic arthritis; also skin of six nonrheumatic atopic persons and 41 nonrheumatic nonatopic persons; he used bacteria "related" and unrelated to rheumatism. He showed again that "arthritic patients" are especially sensitive to streptococci, particularly hemolytic streptococci, but not to staphylococci or gram-negative bacteria. However, there was no evidence that hemolytic streptococci were "specific"; since the positivity of tests was directly proportional to the content of nonspecific irritant substances, such skin tests are of no etiologic or therapeutic value (Traut).

3. Antifibrinolysins. The presence of antifibrinolysins in a patient's plasma presumably means that he has been a fairly recent victim of hemo-

lytic streptococcal infection (Tillett and Garner 1933). Reputedly most patients with rheumatic fever exhibit antifibrinolysis, those with atrophic arthritis do not. However, Waaler has concluded that the reaction is not specific, and antifibrinolysis does not prove that a hemolytic streptococcal infection has been experienced. The majority of seven cases of rheumatic fever showed definite antifibrinolysis, but some antifibrinolysis was present in 50 per cent of 24 cases of atrophic arthritis, and in some cases of subacute bacterial endocarditis from fecal and green-producing streptococci (but not in five cases of Still's disease). The strength of the reactions varied with the severity of the diseases studied.

4. Precipitin tests. Group A hemolytic streptococci contain three known fractions: (1) a nonspecific nucleoprotein—the P fraction; (2) a carbohydrate or C fraction, regarded as group-specific; (3) a type-specific fraction which is a protein substance called the M fraction. The type-specific fraction of group B hemolytic streptococci is a carbohydrate called the S fraction. The presence of antibodies against the C fraction (anti-C precipitins) suggests, but by no means proves, that a patient has been infected with hemolytic streptococci of the corresponding group. Many patients with rheumatic fever possess anti-C precipitins but so do some normals and some patients with other articular diseases, according to Chasis and McEwen (1936). In an attempt to explain the reason for peculiar cross precipitin reactions, Chasis and McEwen studied reactions obtained with crude C-extracts of hemolytic streptococci of various groups (not just group A) in a variety of diseases as well as in immune rabbit serums. Cross-reactions were obtained, due probably to the presence in these serums of antibodies against a nongroup-specific fraction or radical present in the bacteria and in the C-extracts. Chasis and McEwen concluded that this substance is not the nucleoprotein or P fraction and is probably nonproteic.

[This highly technical report throws doubt on the reliability of precipitin tests done with C extracts and indicates that precipitin tests with a C-extract from only a single group must be interpreted with caution.—Ed.]

5. Complement. The complement titer of normal persons and of 33 patients with nonrheumatic complaints was found by Rachmilowitz and Silberstein to vary between 0.04 and 0.06 c.c. The amount of complement in blood was found to be low in active rheumatic fever (complement titers 0.10 to 0.25, av. 0.14 c.c. in 14 cases), but normal in inactive rheumatic fever (6 cases) and in acute atrophic arthritis (13 cases). The determination of blood complement may therefore help to differentiate the polyarthritis of acute rheumatic fever and that of acute atrophic arthritis. The blood complement is low in certain allergic diseases; hence, from their results these workers deduced that rheumatic fever is allergic and that atrophic arthritis is not.

[Complement in human serums does not remain constant in amount even for 24 hours. Without much more work these conclusions seem premature.—Ed.]

No new studies on blood cultures, agglutinins or antistreptolysins in rheumatic fever were reported.

Virus theory. Older studies on the virus theory of rheumatic fever were unacceptable because the material presumed to be etiologic could not be proved to be infective. In 1935 Schlesinger, Signy and Amies obtained, from rheumatic exudates, bodies morphologically similar to elementary bodies from known viruses. Although they also were unable to prove their infectious nature this work seemed significant because the bodies were specifically agglutinated by serums of rheumatic, but not by that of nonrheumatic, patients. Exudates of nonrheumatic patients also contained similar looking bodies but they were not agglutinated by rheumatic serums. This work has been confirmed and extended by Eagles, Evans, Fisher and Keith. Particles resembling virus bodies were found in various materials in cases not only of rheumatic fever but also of atrophic arthritis and chorea. Only a few particles, unsuitable for agglutination tests, were found in blood, urine, subcutaneous nodules, spinal and ascitic fluid but particles were readily found in pleural, pericardial and synovial exudates and were specifically agglutinated, suggesting that they were true virus bodies. Furthermore, not only were they agglutinated by the serums of patients suffering from the disease from which the suspension was prepared, but there was considerable cross-agglutination within the group of rheumatic diseases, suggesting that rheumatic fever, atrophic arthritis and chorea are very closely related etiologically, at least serologically.

[These studies have aroused considerable interest. The work has been well done but its significance is not established. The infective nature of the bodies remains unproved; in the absence of such proof some consider their agglutination as providing evidence less impressive than the immunologic data which incriminate hemolytic streptococci.—Ed.]

Protozoan infestation. According to one writer,[660] acute rheumatism is " due to a protozoan of which the Aschoff body is the encysted form. This protozoan is introduced by the bites of insects in the late summer or the autumn; e.g., harvest bugs or midges." The author claims to have proved " that all cases of acute rheumatism and chorea occur in the children of the acid class, and of this class alone."

[This is a restatement of the writer's previous but uncited work, given here without proof.—Ed.]

Vitamin deficiency. Rinehart summarized the work of himself and colleagues (previously reported in these Reviews).

According to him, the concept that vitamin C deficiency may be a factor in the cause of rheumatic fever is based on strong experimental evidence. Lesions essentially similar to those of rheumatic fever were produced experimentally by the combined influence of infection and vitamin C deficiency. The factor of infection is in no sense minimized. The main pathologic changes in both rheumatic fever and scurvy involve connective tissue. The concept would explain the hemorrhagic and other features of rheumatic fever, including its epidemiologic peculiarities. The blood

plasma in rheumatic fever is low in vitamin C. In brief, experimental, clinical, epidemiologic and biochemical studies all point to the possible importance of vitamin C deficiency in the etiology of this disease.

Further evidence that patients with rheumatic fever are deficient in vitamin C was provided by Abbasy, Hill and Harris. Persons on a " minimal-optimum " dose of vitamin C (25 mg. per day per 140 lbs. body weight) excrete about 13 mg. per day per 140 lbs. body weight. The average daily urinary excretion by 107 patients with active rheumatic fever (or with active tuberculosis) was only 9 mg.; by 86 convalescent rheumatic patients, 10 mg.; but by 64 controls well over 13 mg.; all groups receiving well over the minimum standard amount of the vitamin. The " simplest explanation " was that patients with active rheumatic fever obviously need more vitamin C (since they hold it back) than convalescent rheumatics who in turn need more than normals. [This argument is not necessarily sound; nephritics hold back urea but they don't need it.—Ed.] Does this vitamin C deficiency (or vitamin need) cause or result from the disease? These workers concluded that since patients with tuberculosis and other infections also disclose a deficient excretion (symbol of a need or deficiency of vitamin C) the deficiency may be the effect rather than the cause of active rheumatism. Nevertheless, for reasons given, vitamin C therapy in rheumatic fever was advocated.

Race found evidences of deficiency in both vitamins A and C in patients with subacute rheumatism (and other rheumatic diseases as well, especially in atrophic arthritis).

The vitamin A content of serum ranged from 75 to 140 gammas per 100 c.c. in 14 controls, from 15 to 90 gammas in 10 cases of subacute rheumatism (from 10 to 70 in 14 cases of atrophic arthritis, 10 to 120 in 10 cases of fibrositis, 80 in one case of gout, 90 in one case of hypertrophic arthritis). There was a serum deficiency not only in vitamin A but also in carotene, a precursor of vitamin A. In the rheumatic cases the icterus index and the serum bilirubin content were definitely subnormal; however, the chief cause of the low icterus index was not the reduction in serum bilirubin, which was slight, but an associated reduction in other serum pigments—carotene, a precursor of vitamin A, and xanthophylls, which are not precursors of vitamin A.

The median concentration of vitamin C (ascorbic acid) was 1.03 mg. per 100 c.c. plasma in persons on a diet high in vitamin C; 0.62 mg. in those on a diet " sufficient " in vitamin C, but only 0.39 mg. in those with subacute rheumatism (0.38 in atrophic arthritis; 0.36 in fibrositis; 0.41 in hypertrophic arthritis).

[The numbers of cases studied were small but the results were definite and well controlled.—Ed.]

No final conclusions as to significance were made but Race stated: " Although a vitamin C deficiency may produce some symptoms in man that simulate to some extent those occurring in rheumatic diseases, the clinical picture as a whole is quite different, and more conclusive evidence must be

forthcoming before the hypothesis that these diseases may result from a streptococcal infection superimposed on a vitamin C deficiency can be accepted."

Conclusions on Etiology. Poynton expressed the belief that juvenile rheumatism arises from streptococcal infection but not from that in any local focus, and held that " it is as rash to call rheumatism an allergic disease as to claim it is a diathesis." Connor reminded us that one attack of scarlet fever confers considerable immunity but an attack of erysipelas or rheumatic fever increases one's liability to other attacks; yet all are presumably due to hemolytic streptococci. In spite of these immunologic differences many agreed that there was strong evidence that rheumatic fever is etiologically related to beta (but not to alpha or gamma) hemolytic streptococci.[139, 557] [The serologic work of many has led to such a conclusion, and Coburn and Pauli (1932 et seq.) and others have noted that the nasopharyngeal infections which precipitate rheumatic fever are mostly due to group A hemolytic streptococci. If this is so why is sulfanilamide (which is so effective against many group A hemolytic streptococci) so ineffective in rheumatic fever? To some (e.g., Cushing) this forms a strong argument against a direct relationship between rheumatic fever and hemolytic streptococci.—Ed.]

Treatment of Rheumatic Fever

General Remarks. General principles in treatment were reviewed.[415, 588, 615] It is most important that the victim and his relatives first understand the fundamental chronicity and seriousness of the disease. Too often treatment fails because of its too brief use rather than because of its inherent inadequacy.[615] Since long (1 to 10 years) spontaneous remissions frequently feature the disease one must not hastily give credit to any therapy which is followed by a relatively short period of relief.[728] The scheme of the London County Council includes provision of special rheumatism units for prolonged hospital treatment, establishment of centers for early diagnosis and supervision of quiescent cases, a system of supervision of patients discharged from hospital units, amelioration of unsatisfactory home conditions and central coördination.[679]

Rest. The theme of all was rest, more rest and still more rest for rheumatic patients, especially those with signs of active or impending carditis; rest until all manifestations of active disease disappear and then for at least two or three weeks longer. The ideal treatment of rheumatic carditis would be to stop the heart entirely, to prevent endocardial and myocardial strain until healing occurred. This being impossible, physical and mental rest are imperative; all else is subordinate (Marsh).

To rest and slow the heart some used digitalis when cardiac insufficiency or persistent tachycardia are present.[588, 700] According to Cushing rest over long periods can be overdone. When signs of rheumatic activity cease, graduated activity is in order. Lightwood's scheme was: " (1) patient lying down, one pillow, fed by nurse; (2) two pillows, patient semirecumbent, allowed to feed himself; (3) patient sitting in bed; (4) patient dressed

and allowed on a couch, later walking a few steps; (5) up half time; (6) up all day."

Salicylates. These were considered useful and safe by most writers but of limited value by Eason and Carpenter and by Rosenberg who reviewed salicylate therapy briefly. About 30 cases of methyl salicylate poisoning (18 of them fatal) have been reported since 1799. Lawson and Kaiser reported the death of a child with rheumatic fever who took not over 60 grains of salicylates by mouth and had in five days a total of 3 ounces of oil of wintergreen applied to her knees; dyspnea, vomiting, cyanosis, delirium, acidosis and death three days later occurred. At necropsy the heart was "grossly normal."

Gold. Results from a "limited trial" of gold salts were disappointing to Sherwood.

Sulfanilamide. Marked relief in a few cases of "acute febrile polyarthritis" treated with "prontosil I" was reported from Germany by Veil (1934) and Scheurer (1936). The results of others, however, have been unfavorable. A fatal agranulocytosis affected a 53 year old man with acute rheumatic fever given prontosil album (3 gm. daily for 18 days) by Young. No definite effect was noted by Basman and Perley and by McQuarrie in two cases each, by Hageman in one case, and by Brown and Bannick in an unstated number of cases.

[Attention is called to the current experiences of Swift, Moen and Hirst (1938): to eight patients with rheumatic fever sulfanilamide was given in as large doses as could be tolerated; no beneficial effect was noted, indeed the patients seemed specially susceptible to toxicity therefrom. "The toxic action of sulfanilamide in active rheumatic fever so far outweighs the beneficial therapeutic effect that its administration to patients with this disease does not seem justified."]

Treatment of Tonsillitis and Nasopharyngitis. "Without tonsillitis or pharyngitis there would be little if any rheumatism"; this was the view of Lightwood who painted infected tonsils with protargol and gave potassium chlorate by mouth: He further stated, "If tonsils are irrevocably infected they should be removed; the tonsillar glands and a history of sore throats are our best guide." Others agreed that infected tonsils should be removed as soon as possible.[306, 435] Too often they are removed simply because they are large; the size of tonsils is no index of their infection.[211, 435] Tonsillitis and sore throats are by no means a constant symptom of streptococcal nasopharyngitis. Tonsillectomy often fails to prevent recurrences or ameliorate the condition (Cahan). It had no appreciable effect on the acute streptococcal nasopharyngeal infections seen by Bradley.

Vaccines, Serum. The value of vaccines remains unproved (Jordan). The immediate effect of serum in 44 cases seemed good to Eason and Carpenter; 30 c.c. of Parke Davis' concentrated antiscarlatinal serum were given intramuscularly and repeated within 36 hours. Patients generally became afebrile in about three weeks. [Untoward reactions occurred very occasionally; to prevent these a few minims of adrenalin solution (1:1000) are now

given with each injection of serum.—Ed.] The effects of serum and salicylate were compared. Serum prevented more relapses, was effective in cases resistant to salicylates but was accompanied by longer fever and occasionally by serum sickness or other reactions. The effects of serum may be partly due to its foreign protein content, but more relapses occurred in a few cases in which treatment was by similar amounts of foreign protein without serum.

[This report is interesting but serum therapy must be evaluated in a larger series of cases observed for a longer time.—Ed.]

Transfusions. Rosenberg reported the case of a nine year old boy in his sixth attack who after 12 weeks of continuous fever and a persistently high sedimentation rate was given seven transfusions of blood (each 100 c.c.). The sedimentation rate and fever then dropped progressively and the patient improved decidedly. Similar results were noted in the literature. [The result would have been more impressive had not slight clinical improvement and a slight drop in temperature (but not in the sedimentation rate) been noted before the first transfusion. Further observations are desirable.—Ed.]

Diet and Vitamins. Although the use of vitamin C produced results "encouraging" to Rinehart (1936), others noted therefrom no reduction in the incidence or severity of the disease.[4] Abbasy, Hill and Harris expressed the belief that vitamin C therapy is "likely to be helpful," and that its prophylactic and therapeutic value should be investigated further. Diets high in calories and excessive in vitamins A, B, C, and D were given by Sadow, Hubbard, and Jones to 31 rheumatic patients for an average of 20 weeks; except for increases of weight no benefits were noted. [However, the group receiving the special diet were sicker than the 25 in the control group.—Ed.] Rinehart's answer to such results follows: Too much must not be expected of vitamin C therapy as we are dealing with something much more complex than a simple deficiency. If vitamin C deficiency prepares the soil for an infection to produce rheumatism, the deficiency is only contributory. Valvular deformities would never be anatomically corrected by vitamin C therapy. The most that could be achieved would be restoration of tissues to a state in which they could resist the injurious influence of infection. Prolonged studies are necessary to determine its prophylactic and therapeutic value.

Fever Therapy. This was considered valuable by Simmons. Of nine cases of acute rheumatic fever with active endocarditis six became inactive in an average of 24 days following an average of five treatments. Three cases of endocarditis and chorea became inactive in an average of 46 days after an average of nine treatments (2.5 to 4 hrs. at 103 to 105° F.). [The cases have not been observed long enough to note the effect of treatment on prevention of recurrences and complications.—Ed.]

Special Treatment for the Heart. Rothbart gave repeated intravenous injections of 15 to 20 per cent dextrose to "improve the heart's nutrition." It "did no harm" and seemed to relieve the acute abdominal pain and vomiting associated with acute pericarditis. Roentgen therapy seemed

valuable to Levy and Golden who observed during a period of 11.5 years 48 patients so treated. Cases with low grade activity and no congestive failure were most benefited. The therapy relieved cardiac pain in those without aortic insufficiency, produced no harmful effect but some unpleasant radiation reactions. Cardiac failure can often be prevented or postponed by attention to its premonitory signs: fatigue and limitation of activity through breathlessness (Felter). Attention to heart size is more important than that to heart sounds.

Institutional Care and Climate. Living in the South several months hastens recovery from individual attacks but when patients return North their future course is not significantly altered. To be helped materially children should spend their entire childhood, at least until puberty, in the South; unfortunately this is impracticable on a large scale (Hedley, Wilson). Although favoring convalescent cardiac hospitals and vocational guidance in schools, Hedley did not recommend special schools or classes for rheumatic children: "The psychological effect is bad. It is better to enroll them in schools near their homes and to limit their activities according to their functional capacity." Others favored rheumatic colonies and schools near all large towns and cities.[698]

Prophylaxis. Recommended were isolation of rheumatic children with active disease from intimate contact with other children but particularly from persons with respiratory infections [306, 415]; after-care so that children are not returned to the same conditions of poverty and overcrowding which fostered their disease,[698] governmental grants of adequate food to impoverished children [64]; a wider use of prophylactic schemes like that of the London County Council.[164]

Sydenham's Chorea

As in previous years, the reported incidence of chorea with rheumatic fever varied markedly—from 1.5 per cent to 44 per cent. [Is this a true difference in incidence or a matter of proper recognition?—Ed.] In Australia "choreiform motions" affected only 1.5 per cent of Maddox' 428 juvenile patients with rheumatic fever. Chorea affected 8.5 per cent of Chinese patients,[107] 25 per cent of 488 patients with juvenile carditis in New York,[587] 29 per cent of 73 rheumatic patients in Boston [447] and was the first symptom of 44 per cent of 516 rheumatic children in Edinburgh.[698] Chorea was 33 times more frequent in Chicago than in Galveston.[611] The likelihood of patients with chorea developing progressive rheumatic symptoms and carditis is not clearly established. Warner's patients with chorea seemed to escape carditis more frequently than those with other rheumatic symptoms. Among Wallace's patients, those whose first rheumatic symptom was chorea developed rheumatic recurrences less often than those whose first symptoms were from joints or heart. However, in Wilson's group the type of rheumatic symptoms first noted (aside from carditis) carried no prognostic significance.

Relationship to Rheumatic Fever. Although many rheumatic patients develop chorea and many choreic patients develop carditis and other rheumatic symptoms the connection between chorea and rheumatism has not been settled. Some regard chorea as (1) a symptom of rheumatic fever (e.g., Jones and Bland, 1935); (2) a symptom of several diseases, among them rheumatic fever; (3) an independent disease which may accompany rheumatic fever. The first view was supported by three reports.[523, 587, 724] Among 112 choreic children, Parish, Taran and Starr noted the development of carditis in 53 per cent of 78 cases of "pure chorea" (onset with no other rheumatic symptom), and in 76 per cent of 34 "mixed cases" (chorea with other rheumatic symptoms). Esophagrams showed the incidence of carditis to be even more nearly equal in the two groups. Doubtless nonrheumatic irritants may initiate choreiform symptoms in certain cases, but since the incidence of carditis in pure chorea is almost as high as that among children with the rheumatic diathesis, it was assumed that chorea is of rheumatic origin. Williams' conclusion was similar: Among 142 choreic children were 41 (29 per cent) with, and 101 without, evidences of rheumatic fever. Of 66 choreic children especially studied, 62 per cent had pure chorea, 29 per cent had chorea with carditis, and 9 per cent had chorea but later carditis developed. Recurrences of chorea did not predispose to carditis. It was impossible to tell which choreic child would have rheumatic complications. Chorea frequently accompanied rheumatic carditis, and polyarthritis and carditis were "not uncommon complications" of primary chorea in cases seen by Roth, Lingg and Whittemore but they believed that valvulitis associated with chorea is not due to chorea but to accompanying or intercurrent episodes of polyarthritis and carditis.

The view that chorea and rheumatism are independent was upheld by Coburn and Moore. Of 114 choreic patients studied 2 to 10 years, 30 per cent had no (other) evidence of rheumatism. Of another group of 137 cases of chorea, in approximately half chorea developed repeatedly but no evidence of rheumatism; sedimentation rates and leukocyte counts were persistently normal, there was no familial rheumatism and attacks were precipitated by psychic trauma, not by respiratory infections. Of the other half (68 cases) chorea developed in 29 during quiescent, and in 39 during active, rheumatism. Thus "half of all cases of chorea in New York may occur in individuals not susceptible to rheumatic fever." The physiologic background prerequisite to the development of chorea "may be prepared by a number of abnormal conditions but is especially well prepared by the rheumatic state. This accounts for its frequency in rheumatic patients." But the factor which initiates chorea can be independent of rheumatism and "chorea is not pathognomonic of active rheumatism." A case of Dawson-Walker and Brewis illustrated this point: A boy, aged 12 years, had severe diphtheria, then bulbar paralysis, Sydenham's chorea and multiple peripheral neuritis "as the result of the action of diphtheria toxin on the basal ganglia and higher centers." No previous rheumatic history or manifestations were apparent.

Other Clinical Data. Sex incidence for girls was 56 per cent in one group [724]; 53 per cent in another.[523] Of Williams' cases, fever was absent in 62 per cent, slight in 17 per cent, definite (100° F. or more) in 21 per cent. It was again emphasized that in chorea sedimentation rates are normal unless other rheumatic signs are present.[13, 123, 224, 724] Evans noted obesity complicating juvenile chorea and considered it "post encephalitic obesity, possibly with degeneration in the suprapituitary region."

Treatment. The use of calcium gluconate, grains 15, and acetylsalicylic acid, grains 10, every four hours seemed to shorten the chorea in 23 of Pearson's cases but the idea of Mutch (1934) that chorea was due to a low concentration of calcium in spinal fluid, correction of which cured chorea, was not confirmed.

Fever therapy continues to be the method of choice in chorea. Although there is no definite evidence that it influences the subsequent appearance of carditis; results, generally excellent, were reported in about 80 cases. Barnacle, Ewalt, and Ebaugh treated 45 patients, 19 (42 per cent) with active carditis. Prompt recovery occurred in 37 cases, marked improvement in eight. At the follow-up (two years or less) of 40 patients, 36 were still well, four had had recurrences. Carditis was not a contraindication, indeed it was benefited. Of those with carditis the immediate effect was recovery therefrom in seven, improvement in eight, none in four; late effects in 12 were six cured, six improved. Patients received a total of 40 hours (av.) of fever during (av.) 13 treatments. Of 11 patients treated by Schnabel and Fetter eight were promptly cured, two markedly improved, and one boy died of uncontrollable fever after one treatment. Results were often excellent after only one or two treatments but three to five were usually given. At the follow-up (2 to 7.5 mos. later) eight were well, two had had mild recurrences.

All of five patients given one to 11 sessions of fever by Kendall and Simpson were promptly cured and there were no recurrences. Mitral murmurs present in three cases disappeared. Of eight patients treated by Spekter and McBryde, five obtained good results; one moderately good results and two, indefinite results. Three choreic patients with active carditis received nine (av.) sessions of fever from Simmons: all became free of chorea, fever and pain within 46 days. An excellent result from one session of fever (5 hours at 105° F.) was noted in one case of Solomon and Kopp. A patient with chorea and active carditis received five sessions (5 hours at 105 to 106° F.): Williams [724] stated that the signs of carditis (tachycardia, first degree heart block) disappeared six days after the last session of fever. Most of these workers used artificial fever, each session being 2.5 to 3 or 4 hours at 105 to 106° F., sometimes at 104 to 105° F. (rectal). Some gave five hours of fever at 40 to 40.5° C.[641] Humphris used fever from short waves. Rothbart had "singular success" from 10 to 15 daily intravenous injections of triple typhoid vaccine. The latter was also considered by Spekter and McBryde easier to give and as good as

artificial fever. Long (two to three hours) hot tub baths cured two of three patients of Lowenburg and Nemser. The water was first heated to 85 to 95° F.; then to 105 to 110°; the patients' temperatures rose to 103 to 104° F. An average of 12 daily baths was given. One patient who had valvulitis noted no ill effects.

One death from artificial fever and one from fever induced by typhoid vaccine occurred. After only 1.5 hours of fever (first session) a 12 year old boy had shock and uncontrollable fever and died in 17 hours. Carditis was not noted clinically or at necropsy; cerebral edema and venous congestion were found.[599] Parish, Taran and Starr treated 112 children with rest, warm baths, sedatives and, in 20 cases, typhoid vaccine: 105 were improved, three unimproved and four died; of the latter, three died in acute decompensation, one child died in the course of uncontrollable fever (110° F.) shortly after the fourth injection of typhoid vaccine.

Chronic Arthritis: the Great Types

Clinical Relationship. No interest was exhibited in arguing the relationship of the two great types of chronic arthritis, atrophic and hypertrophic, one to the other. Without discussion, most writers treated them as different diseases. Others[473, 539] still balked at a final separation and expressed the belief that the two may have certain "basal features" or "many etiologic factors in common" even though their clinical and pathologic differences are obvious. The majority made no place for a third type but regarded "infective arthritis" as synonymous with, or at most a clinical variety of, atrophic (rheumatoid) arthritis. Others considered "infective arthritis" distinct and thus that there are three, not two, great types of chronic arthritis.[169, 604] Crowe summarized the supposed distinction briefly: atrophic arthritis generally affects young women, involves small, rather than large joints, produces characteristic symmetrical swellings, trophic changes, muscle atrophy, and, in roentgenograms, general decalcification of bone with slight loss of cartilage but no bone proliferation or destruction. "Infective arthritis" differs from atrophic arthritis "in nearly every respect"; a generalized disease with joint manifestations, its lesions are not symmetrical; metacarpophalangeal rather than interphalangeal joints are likely to be involved; severe destruction of bone often occurs but not generalized decalcification of bone.

[We cannot subscribe to this distinction.—Ed.]

Roentgenologic Differences. The value of roentgenologic differentiation was debated. Roentgenologists are likely to believe that great reliance can be placed on roentgenographic differentiation although it should be correlated with clinical findings.[604] But most rheumatologists do not make the proper use of roentgenography. According to Scott roentgenograms are made "more from curiosity than anything else." No effort is made to standardize position or technic and interpretation is superficial, generally

made by unqualified persons. At least 10 per cent of persons sent to a roentgenologist as having " rheumatism " do not have that disease but have sarcoma, metastatic carcinoma, Paget's disease, Charcot's disease, enchondroma, renal disease, etc. Buckley [85] was fearful lest " the cursory examination of an x-ray picture may displace the clinical study which is the most important." " The most skilled interpretation of a radiograph is of no service if divorced from the clinical study of the case as a whole, and differential diagnosis based on trifling differences in roentgen-ray appearances may only lead to error in prognosis and treatment." He concluded that in a study of atrophic arthritis " x-rays are of little importance as a guide to the management of a case."

The rôle of roentgenology in chronic arthritis was critically appraised by a roentgenologist, Fineman, who studied many types of arthritis in connection with clinical data. In " typical cases," in which articular changes are advanced enough for features to be characteristic, roentgenograms may be adequate for a tentative roentgenologic diagnosis of atrophic or of hypertrophic arthritis but very often the roentgenologist cannot distinguish between them without great difficulty, if at all. In the various types of arthritis changes depend on the duration of the disease, joints involved, age of the patient and many other factors. Most roentgenologists currently believe that articular changes due to trauma or specific infections, or due to neuropathic, endocrine, metabolic and chemical disturbances, are not sufficiently pathognomonic for an etiologic roentgenologic diagnosis. " In chronic arthritis of every type the roentgenologist is often faced with insuperable difficulties when he attempts etiologic classification solely on the basis of roentgen findings. The pitfalls are numerous and mistakes in diagnosis are frequent." The final diagnosis should be made only after consultation with the clinician and correlation of all known facts. " In the final analysis the clinician must still, in most instances, rely on his clinical judgment for the etiologic classification of chronic arthritis." However, the roentgenologist can be of distinct aid in demonstrating focal infection, and Fineman outlined the roentgenologic features indicative of infection in various foci.

Constitutional Relationships. Booth studied the personality of 43 patients with chronic arthritis, their childhood problems and development, the psychologic problems and traumatic influences which closely antedated their arthritis, results of the Rorschach test, etc. A close etiologic relationship between psychologic disturbances and the onset, localization and progression of arthritis was seen.

[Having stated that of the patients studied 25 had rheumatoid, and 18 had osteoarthritis Booth thereafter ignored the distinction completely and gave no analysis of the psychologic differences of either type separately. No attempt was made to study a control series of cases of one or several other incapacitating chronic diseases. It seems to us the writer went to extremes in developing his thesis. If the proper significance is to be attached to psychological factors in arthritis such studies should be made with the closest coöperation between the internist and the psychiatrist.—Ed.]

Atrophic (Rheumatoid, Proliferative, Infectious) Arthritis

Incidence: Race, Age. American Indians of the Southwest are not exempt from the disease: Among 2700 adult Pima Indians who had spent their entire lives on the Arizona Reservation two had atrophic arthritis (Dunham and Montross). Some hold that atrophic and hypertrophic arthritis are different expressions of the same disease at different ages: The chief objection to this idea is that atrophic arthritis, similar in all respects to that of young persons, may affect persons 60 to 70 years old.[473]

Subtypes. The British National Committee subdivided rheumatoid arthritis into (1) rheumatoid arthritis with associated factors (i.e. focal infection); (2) rheumatoid arthritis with no known associated factors. [We have discussed this in previous Reviews.—Ed.] Cecil considers this distinction "intriguing but unjustified" since both present about the same pathologic, clinical and immunologic responses and only "differ" as to whether or not a focus of infection is found (a point of debatable significance). But Warren, Hinton and Bauer separated "typical" from "atypical rheumatoid arthritis" by the absence in the latter of the characteristic history, habitus and physical conditions usually seen in the former. Features presumably distinctive of the atypical form were its presence in sthenic rather than asthenic persons, generally sudden onset after infection without other prodromes, frequency of obvious foci, asymmetrical involvement often of large joints, frequent response to salicylates and long remissions; hence, a better immediate prognosis.

This is the distinction made by those who separate "infective arthritis" definitely from atrophic or (ordinary) rheumatoid arthritis. Crowe considered true rheumatoid arthritis a rare disease, present in only 254 of 2704 cases recently seen, the other 1019 being of osteo-arthritis. [This seems to indicate either a practice specialized among elderly arthritics or else a differentiation not similar to that of most American clinicians.—Ed.] Scott also differentiated, roentgenologically, "infective arthritis" from rheumatoid arthritis but his differentiation seems arbitrary and ambiguous in the light of his case 2. Roentgenograms of a patient with the "typical clinical picture of rheumatoid arthritis" (spindle joints, etc.) disclosed no generalized disturbance of bone calcium. Hence, Scott called it "infective arthritis, not rheumatoid." But signs of "toxic thyroid" were later disclosed "and with appropriate treatment complete recovery resulted."

[The propriety of applying the term "infective arthritis" to a condition supposedly due to thyroid toxicity seems questionable.—Ed.]

Clinical Data: Symptoms, Course, Prognosis. The necessity of establishing definite criteria for the identification of atrophic arthritis was stressed by Cecil whose criteria follow: 1. Data considered essential were fusiform fingers, the most characteristic early lesion, and polyarticular involvement. 2. Data considered very helpful in diagnosis, and usually or often but not always present were positive agglutination tests for hemolytic streptococci,

subcutaneous nodules (larger and more persistent than those of rheumatic fever) the pathologic reactions of which nodules are " almost pathognomonic of the disease," and demonstration of the typical pathologic change of articular tissue removed at biopsy when possible. 3. Data considered nonessential, frequently present but not consistently enough to be reliable, were vasomotor disturbances, muscle and skin atrophy, presence of antistreptolysins and precipitins, rapid sedimentation rate (not specific) and " characteristic " roentgenographic changes (absent in early stages).

Subcutaneous nodules, varying greatly in size, accompany the disease in 20 to 30 per cent of cases (rarely or never in hypertrophic arthritis) according to Miller, but in only 4 to 5 per cent of cases according to Cecil. They usually develop at pressure points—near an elbow over the ulna, when the ulna is used to bear weight, because the wrist on that side is arthritic; over the occiput or spine of thin, bedridden persons.[133] Cohen noted a point frequently mentioned but inadequately studied: The increased pains which precede storms usually disappear when the rain actually begins. Crowe discussed the variability of pain: Regardless of etiology, symptoms are due to reaction of joint tissues; the greater the reaction, as a rule the more the pain. " In conditions of poor health or of illness joint tissue reaction is less, [not entirely clear as to meaning or as to how it is demonstrated.—Ed.] hence the pain also is less, and in fact during an intercurrent illness such as influenza, swellings and pains may for the time disappear altogether."

Data on the course and prognosis of the disease among children are meager; hence those of Colver are of special interest.

Sixty-nine children were studied " since the war "; 60 per cent were girls. Age of onset was: less than one year in two cases; at the age of one year in eight; two years in 14; three years in six; four years in 12; five years in four; six years in four; seven years in four; eight years in five; nine years in two; 10 years in six. [The chart is not clear; this totals to only 67, not 69 cases.—Ed.] Of 49 patients followed (for an unstated time) 12 were dead, 18 had active and 19 had quiescent arthritis. The disease was apparently self-limiting, lasting an average of nearly five years; never more than seven years. The disease of 19 was " cured " or quiescent; of these, eight were crippled in one to four joints; four were practically cured, having only occasional slight discomfort on full motion; seven were completely cured. Thus, complete recovery was frequent among those whose disease lasted two to three years but when it lasted more than three years recovery was never complete. It can be expected that " approximately one in four recover completely." [This is not the experience of some of us.—Ed.] Gross crippling was uncommon; all but two patients could earn a livelihood; all but one could walk. In no case did symptoms recur after 18 months of quiescence.

In the course of the active disease, a mid-diastolic murmur developed in one case; one patient had adherent pericarditis; " none of the old cases " had valvulitis. " There is no period in life when the onset of rheumatoid arthritis may not be associated with glandular enlargement " but adenopathy and splenomegaly were common in this group. Among patients affected in the first four years of life, adenopathy was the rule (present in 80 per cent) rather than the exception. In the older cases it was progressively rarer (present in 33 per cent). It had no influence on prognosis. Exacerbations of arthritis were frequently related to nasopharyngitis but removal of foci did not seem to influence the prognosis. The high mortality was remarkable:

Of the 42 children who developed the disease in the first five years of life 12 (29 per cent) died, usually within three years. No deaths occurred among those first affected after five years of age and, if children, no matter how young, when first affected, survived three years of the disease, practically none of them died of it thereafter. Five of the 12 deaths occurred in hospital and were due to extreme progressive emaciation and anemia, terminal lesions being hemolytic streptococcal septicemia in two cases, renal calculus with infection in one, amyloidosis and pericarditis in one, unknown (but pericardial adhesions present) in one. Pneumonia was the cited (but uncertified) cause of death of most of the seven patients who died at home.

The "criteria of cure" noted by Cecil and by Colver were: Partial or complete functional restitution of joints (except for residual thickening or limitation due to ankylosis); absence of pain, swelling, exhaustion, leukocytosis or anemia and absence of an altered sedimentation rate and of specific agglutinins for hemolytic streptococci for at least two years.

Unusual Clinical Features; Effects of Jaundice. Further observations on the inactivating effect of spontaneous jaundice on atrophic arthritis and on primary fibrositis were reported by Hench. Thompson and Wyatt noted the preliminary effects of "induced jaundice" (experimental hyperbilirubinemia) on atrophic arthritis.

[Since these 1937 reports were only in abstract they will not be discussed here: the full reports (1938) will be discussed in the next Review.—Ed.]

In this connection, a case reported by Boros is of great interest: In 1935 a young man was seen who had had ragweed hay fever with severe asthma every August for eight to nine years so badly that it became an "intolerable burden." Desensitization had given no relief. For an unstated time he had had "rheumatic pains" in a leg for which, during 10 months, he consumed 100 cinchophen tablets, never more than three a week. These gave "no actual freedom from pain." He then (August 1935) developed anorexia, malaise and weakness, and shortly thereafter (date not stated) jaundice but no pruritus. Then a "momentous thing" happened; as noted, the entire train of symptoms from which he had been suffering over so many years ceased promptly as jaundice with its attendant hepatic involvement appeared. "During August just preceding the onset of the jaundice the patient had experienced a complete cessation of his hay fever symptoms" and "with the onset of the jaundice all his rheumatic symptoms suddenly cleared up." A year later the [anti-allergic and anti-rheumatic?—Ed.] factors were still operating: He had no hay fever or asthma in August 1936 and even spent two weeks "where the ragweed literally abounded in countless numbers, enjoying his stay in complete happiness and comfort."

[On the basis of his early experiences Hench (1933) considered this phenomenon "relatively specific" for atrophic arthritis and fibrositis but regarded the possibility that the phenomenon might be more basic than an anti-rheumatic one. As he recently stated: "Perhaps the exhibition and application of the phenomenon may be possible in other conditions." The report of Boros seems to strengthen this possibility.—Ed.]

Atrophic Arthritis with Enlarged Lymph Nodes, Spleen and Liver; Still's Disease. When atrophic arthritis affects children aged four years or less, almost always it is accompanied by lymphoid hyperplasia. The accompanying condition is seen less often among older children; with increasing rarity among adults.[136] Since articular changes in late Still's disease are similar to those of late atrophic arthritis of adults, many regard

Still's disease as simply juvenile atrophic arthritis.[126] Kauffman noted six cases of adult Still's disease among 2000 cases of atrophic arthritis; all patients were young women affected at least seven months with arthritis. In sequence there appeared enlargement of cervical, epitrochlear, subinguinal and axillary (but practically never submaxillary) lymph nodes, and of spleen and liver, the latter transiently. Biopsy of lymph nodes disclosed hyperplasia and mild infiltration with round cells. Cyclic exacerbations of lymphatic hyperplasia accompanied increased joint pains, fever, and prostration. Associated features were recurrent acute abdominal pain, nausea and rigidity sometimes simulating appendicitis, lasting 24 to 72 hours; also skin reactions (rheumatic nodules, erythematous blotches or acute urticarial lesions), less commonly hemorrhagic conjunctivitis. The cyclic reactions were at times aborted by injections of triple typhoid vaccine " in the first few hours of the attack." The prognosis was that of ordinary atrophic arthritis.

Collins reported two cases of atrophic arthritis affecting adults, with leukopenia, splenomegaly and hepatomegaly and reviewed the literature thereon. The cause of enlargement of the spleen and liver was not determined. The neutrophilic leukopenia probably was the result of premature and excessive destruction of maturing polymorphonuclears rather than of failure of bone marrow. Injections of pentnucleotide were ineffective. Since the arthritis was identical with atrophic arthritis Collins regarded adult Still's disease or " Felty's syndrome " simply as a rare variety of atrophic arthritis.

[So do we.—Ed.]

Pathology. 1. Joints. The pathologic reactions in synovial membrane (vascular granulation tissue with focal collections of lymphoid cells) seemed " specific " for this disease to Cecil, but not to Fisher, who regarded them as similar to those in rheumatic fever. In addition to the usual changes (proliferation of synovial cells and of vascular endothelium, focal collections of lymphocytes " in the main perivascular ") Fisher found areas of fibrinoid degeneration (first noted in atrophic arthritis by Klinge and Grzimek, 1932) and two changes " not described before "—giant cells of the Aschoff type and sometimes edema of synovial membrane. Collins cited Walker Swift to the effect that the focal lymphocytic collections and synovial proliferations seen in atrophic arthritis sometimes occur in the synovial lining of tendon sheaths in traumatic tenosynovitis.

2. Nodules. Opinions differ as to whether the nodules of atrophic arthritis and those of rheumatic fever are identical. Some (i.e. McEwan 1933, Dawson 1933) believe that they are; others do not. Collins [132] emphasized the differences, rather than the similarities, in the nodules of atrophic arthritis and rheumatic fever: According to Collins the differences are more striking than the similarities, therefore the nodules must be basically different.

The early nodules are similar in both diseases but developmental differences appear. Both reveal fibrinoid degeneration, proliferation of young fibrous and connec-

tive tissue cells, vascular proliferation and peculiar vascular changes. In nodules of rheumatic fever there is always more vascular proliferation and more polymorphonuclear leukocytic invasion and the nodule tends to organization and replacement by normal fibrous tissue after a few months. In arthritic nodules the early size and spread of necrosis is far greater than in the others: "The large spreading focus of necrosis with its deep wall of fibroblasts is characteristic only of the rheumatoid arthritis nodule as is its later development into a fluid-containing cyst with connective tissue lining." Another fundamental difference: Alteration of original collagen is supposedly the earliest change in nodules of rheumatic fever but in those of arthritis connective tissue proliferation precedes the degeneration which subsequently takes place in the new tissue. [One of us, M. H. D., cannot agree with this.—Ed.] Clinical differences also exist: In rheumatic fever nodules occur also in skin, in tendinous expansions and in other sites less exposed to trauma, are nearly always multiple, never attain the size of those in arthritis and disappear with the acute attacks; those in arthritis appear at points of trauma but not in skin, small ones may undergo resolution and cicatrization and disappear, but many persist for years with permanent, bulky scars. The arthritis nodules are different also from those caused by trauma alone.

Roentgenograms. The characteristic features and difficulties in diagnosis were outlined by Fineman.

Laboratory data. The relative value of laboratory data in diagnosis and in estimating activity and prognosis were studied by Short, Dienes and Bauer and by Kersley.[372]

1. Blood counts. Total and routine differential leukocyte counts are of little help in following the course of atrophic arthritis. When the disease is acute and febrile, leukocytosis may occur; in chronic cases the count is normal or low. Often polymorphonucleosis is present early; later, neutropenia with relative lymphocytosis. To study activity and prognosis, Arneth-Schilling counts of filamented and nonfilamented leukocytes are useful: In active atrophic arthritis immature (nonfilamented) cells are increased. In 35 cases 100 tests were done; 87 per cent were positive (young cells more than 8 per cent). They were positive in 65 per cent of patients less than one year old; in 93 per cent of older patients (Short, Dienes, Bauer). Kersley's results were variable: The Arneth count was sometimes high, sometimes low; the shift was usually to the left but sometimes to the right (details not given).

2. Sedimentation rate. This was again considered the most useful test in making an early differential diagnosis and in estimating activity of the disease. Using the Rourke-Ernstene method and correcting for anemia, Short, Dienes, and Bauer noted elevated rates in 92 per cent of 154 tests on 49 patients; rates were rapid in 79 per cent of tests on patients less than one year old, on 96 per cent of older patients. Kersley noted persistently normal rates in a few cases apparently similar to atrophic arthritis. He considered wide-bore tubes more delicate and accurate than narrow tubes and the capillary methods "almost useless." Using the Cutler method, Lautman noted elevated rates (more than 10 mm. in 1 hr.) in all of 118 cases.

Those interested in the numerous physicochemical factors which influence the rates are referred to several instructive papers.[55, 76, 418, 431, 582, 731, 744, 751] Wintrobe recommended reporting both corrected and uncorrected rates; sometimes uncorrected rates are more significant. New methods were suggested.[128, 193] Because rates by ordinary methods are "of very slight value and should be discarded," Crowe recommended the differential sedimentation test of Coke.[128] Bannick, Gregg and Guernsey recommended the simplest technic (tall Westergren tubes) so that the test will be widely used. Mental allowance should be made for the fact that anemia accelerates rates "but a routine correction for anemia in each case is unnecessary."

[Some of us cannot agree.—Ed.]

3. Vernes test. In atrophic arthritis the result of the Vernes resorcinol test on serum is reputedly generally abnormal. Short, Dienes and Bauer found it abnormal in only 58 per cent of 49 cases and less useful than other tests.

4. Saline absorption test. The test was abnormal in 4 of 14 cases; Kersley considered it valueless.

5. Plasma pigments; other blood studies. Race noted that the plasma pigments, bilirubin and carotene, were slightly reduced in atrophic arthritis. The blood glutathione is normal even though the cystine content of nails may be low. Of 60 patients with atrophic arthritis increases were found in blood creatinine in 23 per cent; in urine creatinine in 7 per cent; in blood creatine in 3 per cent; in urine creatine in 30 per cent (Moreno). No interpretation was offered.

6. Glucose tolerance tests. Results of tests were abnormal in only five of Kersley's 47 cases. There was no relation between the height of the curve and the sedimentation rates. Various explanations of the abnormal glucose tolerance tests in arthritis and other chronic diseases have been offered: That these results are due to, (*a*) disturbances of pancreatic function; (*b*) circulatory disturbances, slowing removal of sugar from blood (Pemberton, 1920); (*c*) hepatic dysfunction, the effects of toxemia on liver, not pancreas (Soskin, Allweiss, Mirsky, 1935).

7. Liver function tests. Using the azorubin S excretion test, Rawls, Weiss and Collins found hepatic dysfunction in 55 per cent of 100 cases of atrophic arthritis; dysfunction was present in severe cases more often than in mild cases (73 per cent of severe cases; 48 per cent of moderately severe cases, 25 per cent of mild cases). In most cases showing dysfunction the total serum protein was slightly low; the albumin and globulin ratio reversed.

[This report is interesting but difficult to evaluate. The test used is not one commonly employed. Results with it were not compared to those with standard liver function tests and controls were not studied, except a few cases of osteo-arthritis. The work should be extended.—Ed.]

Etiology and Pathogenesis of Atrophic Arthritis

Factors of Infection. 1. Foci. No new work of significance was done on the relation of foci of infection to atrophic arthritis. Many writers made

the usual general comments and incriminated this or that focus. These will be noted briefly under "management of foci." Foci, generally in throat or pharynx, were present in 58 per cent of Thompson's 343 cases; bacteria most often present were hemolytic streptococci. [No further data were given. —Ed.] According to Heyd "One may reasonably expect that approximately 5 per cent of patients with chronic arthritis have a disease of the gallbladder and that, in these 5 per cent, either the primary or secondary mechanism for arthritis resides in the gallbladder." [No statistical, bacteriologic or clinical proof was offered. Others have noted cholecystitis in 4.5 to 6 per cent of cases of atrophic arthritis (Hartung and Steinbrocker, 1932; Judd and Hench, 1933) but this incidence is no higher than that among any general group of patients seen in large hospitals or clinics.—Ed.] Stabler and Pemberton found abnormal amounts (but not types) of bacteria in the stools of 17 patients with "chronic arthritis." Aerobic and micro-aerobic streptococci were found in all stools. According to Dawson the intestines are the natural habitat of certain hemolytic streptococci. Streptococci are ubiquitous and their presence in nasopharynx, intestines and on skin is "entirely without significance." From a study of 4000 "arthritis patients" (types unstated) Barrows concluded that important pelvic foci were present in 6 to 10 per cent. Among 1000 patients with "arthritis," genito-urinary foci were found by Taylor in 65 per cent of 400 who admitted a previous "genito-urinary history"; in only 5 per cent of those who did not. Sometimes "genito-urinary infection can be the sole cause of arthritis."

[We see no value in discussing these papers in detail. The protagonists and antagonists of the theory of focal infection in arthritis have reached an impasse where those who believe in it "believe" and those who don't, don't. For the former no new "proof" is needed; for the latter no "new" data are convincing. Until really new and strikingly different data are forthcoming, this impasse will continue. —Ed.]

The pathogen selective culture method (Solis-Cohen) was applied by Crowe to 4181 specimens (urine, feces, vaginal swabs, etc.) in 1390 cases, chiefly arthritic. All types of arthritis gave positive cultures; all seemed to be infective, including osteo-arthritis. Crowe concluded that the method is of great value for isolating special organisms for use in vaccine treatment but that it has very little bearing on the pathology of the disease. Only occasionally did it appear that the microbe isolated was the sole infecting organism. There was, as a rule, "no evidence that the microbe isolated is the direct cause of a chronic rheumatism or arthritis, and any focus from which an organism is isolated can seldom be incriminated as the 'causative focus' except in quite exceptional circumstances. Although much weight may be given to the presence of a pathogen selective positive germ in, say, a tonsil or a cervix, in no case must its presence alone be taken as a peremptory call to extirpate that focus."

2. Agglutination tests. Agglutinins to any one of four strains of hemolytic streptococci were found in only 53 per cent of tests done on 49 patients by Short, Dienes and Bauer (in 47 per cent of those less than one year old;

in 55 per cent of others). Only 24 to 36 per cent of the patients of Neil and Hartung possessed agglutinins in significant titer (1 : 160 and more) to certain strains (NY 5, AB 13) but not to other strains of hemolytic or to green-producing streptococci. Early work indicated that serums of most patients with atrophic arthritis agglutinated group A hemolytic streptococci; later, the serums were found at times to possess "cross-agglutinins" with other streptococcal groups. Studying this phenomenon, Wainwright noted agglutination not only of group A, but also of three strains of group B (Lancefield) streptococci. Group specificity rather than strain specificity was apparent for both groups A and B. The phenomenon is probably due to the development of multiple agglutinins for hemolytic streptococci in such cases, rather than to any crossing of the reactions between the two groups. This "does not bar the conclusion that the agglutinins present in these sera are the result of rheumatoid arthritis, and are indeed quite characteristic of the disease, but the true nature of the reaction requires further study." Others [179, 617] pointed out that these tests are technically difficult, impractical as routine procedures, and subject to great error in interpretation. The reaction seems highly characteristic for atrophic arthritis and may represent a specific diagnostic test indicating hemolytic streptococci are primarily or secondarily involved in the disease; however, it may be nonspecific, or rather "specific" for the disease but without etiologic significance (like the Weil-Felix or Wassermann reactions).

3. Precipitin tests. In their cases, Neil and Hartung noted precipitins for hemolytic streptococci in titers comparable to those for agglutinins. They considered precipitin tests superior to agglutination tests. But the former are of no value as routine tests (Dawson). Already noted (under "rheumatic fever") was the work of Chasis and McEwan on cross precipitation reactions in serums of patients with rheumatic fever, scarlet fever, and atrophic arthritis.

4. Antifibrinolysins. These are usually normal but may be increased in early and acute cases. Studies thereon suggest that the disease is sometimes initiated, but not kept up, by hemolytic streptococci (Dawson). Waaler noted increased antifibrinolysis in 50 per cent of 24 cases; the reaction changed with the activity of the disease.

5. Skin tests. Although the skin of patients with atrophic arthritis (also rheumatic fever) is likely to be particularly sensitive to hemolytic streptococci, Traut and Dawson considered skin tests of no value. Post, however, regarded the local and focal reactions due to intracutaneous injections of bacterial filtrates of some significance.

6. Complement. Amounts of complement were normal in 13 cases of variable severity (Rachmilowitz and Silberstein). The test is valueless in arthritis (Dawson).

7. Interpretation of immunologic data. Since progress has not been made in this matter, current comments were few and brief. There is no immunologic evidence that the disease is due to green-producing or indif-

ferent streptococci. Such evidence as there is seems to incriminate hemolytic streptococci but is incomplete, and one cannot conclude that streptococci cause the disease. Perhaps they are the sensitizing (predisposing) agent and some other factor is the direct exciting cause.[39, 86, 179]

Theory of Bacterial Allergy. The sound and the fury thereon have abated, at least temporarily, and nothing new of significance was reported. At present "allergy [as a cause of chronic arthritis] is little more than a hypothesis and a rather unsatisfactory one at that" (Dawson).

Virus Theory. Particles resembling virus bodies were found by Eagles, Evans, Fisher and Keith in material from patients with atrophic arthritis as well as from those with rheumatic fever and chorea. Serums from patients suffering from these diseases agglutinated the suspensions representing the corresponding diseases. Therefore, the particles seemed of etiologic significance even though their infectivity has not been proved.

Factor of Trauma. The rôle of poor posture as a predisposing, localizing and aggravating factor in arthritis was discussed by Hartung.

Factor of Circulatory Disturbance. The most diversified arrangement of nail bed capillaries was noted by Kersley in examination of normal persons and of patients with atrophic, hypertrophic and gouty arthritis. No abnormality was characteristic of any group. Atrophic arthritis has been ascribed to various circulatory abnormalities, among them venous stasis (Bernstein, 1933), varicose veins, phlebitis (Meyer, 1935). To determine what effect, if any, venous stasis has on the production of arthritis, McMaster studied 30 cases of varicose veins of long standing, with prolonged edema of ankles and feet. Roentgenographic evidence of chronic arthritis in ankles and feet was absent in 21 (70 per cent), present in nine (30 per cent) cases but only when there was both passive congestion and ulcerous infection of the leg or near the ankle. Even so, articular changes were mild.

[All but one of the nine patients with arthritis were between 52 and 83 years old; factors of age and trauma may have been responsible for the changes. A control study of a group comparable in age and weight, but without varicosities, should have been made.—Ed.]

Factor of Altered Metabolism. No consistent or significant evidences of disturbed carbohydrate metabolism were noted by Kersley. According to Forbes and Neale (1935, 1936) indoluria is present in most cases of atrophic arthritis, diminishes as patients improve and disappears with recovery. This suggested that indole might be a cause of arthritis (Forbes and Neale[242]). Marked arthritic changes were produced within a few weeks by intra-articular injections, into animals, of indole, skatole, and indole proprionic acid in a solvent. Muscle atrophy, joint swelling, crepitus and stiffness, proliferation and erosion of cartilage and capsular thickening resulted. Control joints, injected with solvent alone, were normal. The indole ring was not responsible since tryptamine (B-indolethylamine) produced no lesions. The results warrant further study but do not prove that products of putrefaction of tryptophane are responsible for atrophic arthritis.

[As the authors pointed out, arthritic changes can be produced by intra-articular injection of a wide variety of mild or strong chemical irritants from distilled water to carbolic acid. Such studies are of interest but do not prove the cause of atrophic arthritis. In these experiments the synovial reaction was not mentioned.—Ed.]

An atonic bowel frequently has been noted in arthritis; it is also a feature of vitamin B deficiency. Steinberg noted certain symptoms (digestive disturbances, lack of vigor, weakness, anorexia) common to both conditions but joint changes do not occur in experimental or clinical vitamin B deficiency. Of 24 patients (mostly with atrophic arthritis) colons of 79 per cent were spastic; of only 4 per cent atonic. [Normal in the rest?—Ed.] The spasticity certainly cannot be blamed on vitamin B deficiency. Non-arthritics were found to consume 2.3 cupfuls of vegetables daily; arthritics almost as much—1.5 cupfuls: "One could hardly surmise that a lack of vitamin B intake was an etiologic factor in chronic arthritis."

Depletion of vitamin C reserve was noted in cases of acute rheumatism, atrophic arthritis and tuberculosis by Abbasy, Harris and Ellman. The average daily urinary excretion of vitamin C was (per 140 lb. body weight) 13 mg. in normal conditions, 8.6 mg. in atrophic arthritis, 7.6 mg. in active tuberculosis; the more rapid the sedimentation rates the less the urinary excretion of vitamin C. This represents an increased destruction of, or a demand for, vitamin C in atrophic arthritis. In infective processes there is increased consumption of vitamin C. Since the results in tuberculosis and atrophic arthritis were alike, the latter disease may also be due to infection.

Race noted in various rheumatic diseases, especially atrophic arthritis, subnormal amounts of the carotinoid pigments and of vitamins A and C. "A deficiency of vitamin B is also probable but has not yet been demonstrated." Admitting that arthritis does not resemble any known specific dietary deficiency, Pemberton nevertheless restated his belief that unbalanced nutrition may, with other factors, pave the way for the production of either type of arthritis.

Factor of Endocrine Abnormality. This idea found no support. There is considerable doubt whether endocrine dysfunction alone can produce atrophic arthritis (Poynton).

Neurogenic Factors. Psychic trauma has been cited by some as a precipitating factor, by others as perhaps the actual cause of atrophic arthritis (Jones 1909, Smith 1932, Nissen and Spencer 1936). Thomas found notable emotional disturbances antedating arthritis in all of 31 cases; in nine cases severe depression developed weeks or months before, and became less marked after, arthritis had developed. The phenomenon was unexplained.

Conclusions on Etiology. It is only too apparent that the year under review recorded no striking progress in the problem of causation. Writers seemed less enthusiastic about arguing their favored theses; perhaps this dissatisfaction with existing hypotheses should, of itself, be recognized as progress. Some regarded the pathologic reaction in joints (no polymorphonuclears, negative cultures) as strong evidence that the disease is not

due to intra-articular germs. In a few cases in which Fisher found streptococci in joints, the pathologic reaction in synovial membranes was typically pyogenic with intense polymorphonuclear infiltrations, representing a secondary infection; in these cases toxic foci were obvious but not in others. The majority of writers still supported the infectious theory as the most likely one but did so rather dispiritedly. Others warned against its acceptance as a bar to progress. "It is curious how easy the recognition of any organism lulls for a time at least the urge for further inquiry: Many workers having isolated a given organism from a focus, from blood or synovia are prepared to accept the findings with such absolute finality that the door of research is closed not only against other obvious causal factors but even against inquiry as to how the germ in question produces its results" (Miller).

Relationship between Atrophic Arthritis and Other Diseases. 1. Rheumatic fever. Some [201, 237] expressed the belief that the relationship between atrophic arthritis and rheumatic fever is extremely close because the articular pathology of the two seemed similar to them and because in both diseases "virus bodies" were found, cross agglutination of which occurred with regularity. "While it cannot be said that their etiology is identical, it is at least probable that they possess some common significant factor which is reflected in serological tests." [201] However, having studied the nodules in both conditions Collins was unable to postulate a pathologic relationship between the two diseases. Master, Jaffe and Dack reported the case of a young girl with chorea, pericarditis, mitral and aortic endocarditis and attacks of migratory arthritis who later developed the characteristic picture of chronic atrophic arthritis (deformities, ulnar deviation, etc.). [The clinical description bears out the distinction drawn.—Ed.] The likelihood of a common etiology was considered but discarded; the combination was considered probably coincidental, two distinct diseases affecting one patient.

2. Still's disease. This was discussed earlier in this review.

Treatment of Atrophic Arthritis

General Remarks. In need of correction is the attitude of those physicians who believe that arthritis is a more or less hopeless problem.[126] In need of sharper correction are those too numerous patients who demand quick cure. Having ignored their physician for months on end while sampling the ancestral and neighborhood "cures" this type of patient finally comes "barging" into the physician's office and sometimes acts as if the physician himself had invented the disease and was personally responsible for its prompt eradication. The physician is expected to "pull a miracle out of his sleeve" or else —. The physician is quite aware of his patient's unspoken words, "I'll give this fellow just so many weeks, after that no more nonsense." Physicians must not be offended by the tactics of such patients; they are sick, distraught human beings who are simply and unconsciously acting on the principle that the best defense is an offense.

But for them especially and for all arthritics the physician should, at an early consultation, make clear what both he and the patient are up against. A tuberculous patient accepts the necessity for prolonged, unspectacular treatment. Similarly, arthritic patients must learn the necessity of a long and perhaps tedious program of useful but undramatic measures. And at the start they must learn what their relationship to the physician is to be. Such is the nature of the disease that although as "quarterback" the physician must "call the signals" it is the patient that must "run with the ball." Unfortunately in this disease the patient cannot yet do as he would like to do—sit comfortably on the bench and applaud the physician's battle. Too infrequently can the physician by some lucky tour-de-force rapidly cure his patient but he can often teach the patient how slowly to "cure" himself. Therefore the first principle is, as Wyatt put it, for the physician to "put all the cards on the table" and unless the patient is prepared to "play the game through to the end" it is far better (for the physician) not to start at all.

In the absence of precise knowledge of etiology, most treatment is symptomatic or empirical but many of the finest treatments in medicine have been based on empiricism.[740] In advancing the cause of the arthritic it is far better for physicians to understand and apply the standard procedures of known value than to accept too hastily the new "cures." The following, written by Pelouze [537] in another connection, is applicable to the field of rheumatism: "In these restless days when every new, near-new or old thing in the way of treatment of disease is scrutinized by our commercial brethren for its dollar making possibilities, it behooves us to place ourselves in a position in which we are not swayed foolishly into heights of enthusiasm that offer our patients but little. Far too often we have been the stepping stones over which the commercially inclined have travelled to their dollar harvests." As McCarty wrote "The only new panaceas and specifics in this condition are quite old: Careful study and long hard work."

Management of Foci. In the literature under review the optimists regarding removal of foci were a shade more numerous than the pessimists. Wrote the latter: It is all too obvious that removal of infected foci does not necessarily cure arthritis [455]; only in a minority of cases can infected foci be found and the results of their removal are mostly disappointing.[740] Wrote the former: There has been too much talk and too little action about removing foci. If foci are removed within six months of the onset of arthritis the patient usually recovers without further treatment.[126] Hamilton advised "radicalism within the limits of common sense" and Haden concluded that focal infection is only an influencing factor, not the one of chief importance. Nevertheless, it is unwise to allow evident focal infections to remain. They should be removed in mild cases early; in more advanced cases when patients are "on the up-grade." Buckley expressed the belief that following removal of foci a sufficient number of complete recoveries have been noted to indicate that such foci may be of etiologic importance.

Removal of foci was never unwise in principle but has been expected to accomplish the impossible.

Wholesale removal of teeth was condemned; no tooth should be removed until a roentgenogram of it has been made. Infected teeth should be removed, also pulpless or partially erupted teeth, if a more definite focus has not been found. Alveolectomy is not a panacea but may be of definite nonspecific value (Dunn). Scott regarded alveolectomy as too often a "ritual" which the "wise men" feel they must observe. Breuning described the local indications for tonsillectomy and considered age per se no contraindication to tonsillectomy. Regardless of age, death had not occurred in the course of 1800 tonsillectomies and Breuning cited the experience of Turnley who had observed 76,000 tonsillectomies without a hemorrhagic death. Electrocoagulation was not advised. In the presence of atrophic arthritis, according to Cohen, "Whenever tonsils are diseased they should be removed; in fact (considering our inability to pre-judge tonsillar infection) whenever tonsils are present they should be removed." According to Hurd, "silent sinusitis" (no headaches or frank pus) is frequently an important focus, eradication of which may relieve joints. When the gall-bladder of an arthritic is presumably diseased, the indications for cholecystectomy must be determined on the basis of the gall-bladder and not of the joints. Taylor expressed the belief that genito-urinary foci were sometimes the sole cause of arthritis. Barrows noted the various surgical and nonsurgical methods of treating pelvic foci. The surgical correction of toxic absorption from cecal stasis was approved by Schmoele.

[Lane's idea (1924) found its firmest American foothold in California; it has been largely abandoned elsewhere. It is difficult to incriminate cecal stasis when atrophic arthritis has, as far as we know, never been reported as a sequel to Hirschsprung's disease. In general, operations for the correction of cecal stasis have had only a transient beneficial effect on arthritics, similar to that of any (incidental) surgical procedure involving anesthesia, rest in bed, postoperative fever, altered diet, convalescence.—Ed.]

[In closing this discussion may we paraphrase some remarks on fever of unknown origin, by Hamman and Wainwright, remarks most applicable to arthritis: The impression has strongly prevailed that [arthritis] is commonly due to hidden foci of infection. This conception has dominated medical practice during the last 25 years. Never before in modern times has a theory of disease so completely captured the imagination of the profession and been so enthusiastically followed in practice. The theory is extraordinarily beguiling, because it explains simply and directly many of the most abstruse and bewildering problems in pathogenesis and still more so because it offers an equally simple and direct rule of practice. No patient can feel neglected while his body is being scrutinized thoroughly and the searching tests of science applied with meticulous care to every function. Nor need any physician be oppressed by the sense of fruitless inactivity so long as there are teeth to be pulled, tonsils to be enucleated, sinuses to be reamed, thyroids to be excised, gallbladders to be drained, appendices to be removed and kidneys to be probed. For a while the practice of medicine became almost solely a routine search for foci of infection and the practice of surgery a routine removal of foci. Science was rampant. . . . Those were the glorious and profitable years, cut short, alas by the onset of the financial depression!]

Vaccines, Antigens, Filtrates. Crowe was convinced that of any single method of treatment vaccines give "far and away the best results." Of 5000 patients given his mixed vaccine, 85 per cent received some benefit (details not given). However, he admitted that other forms of therapy also should be used. Ishmael and McBride "desensitized" 100 patients with vaccines from several strains of arthrotropic streptococci: "88 became pain free and sedimentation rates returned to normal in two months' therapy." Of Banister's 20 patients 19 were "greatly benefited" from intravenous injections of a vaccine made of hemolytic streptococci recovered from the blood in one case by the method of Gray and Gowan (1931). Thompson and Wyatt considered vaccines highly beneficial in a large percentage of cases in which sedimentation rates were high and agglutination titers were low. Vaccines have a definite place as part of a therapeutic program but not as a specific, according to Overholt and Mortensen, who considered stock vaccines of arthrotropic streptococci (e.g. Lederle's *Streptococcus hemolyticus* vaccine) preferable to autogenous strains of unknown tropism. Vaccines were given intravenously in small doses for four to 12 months. Haden saw no objection to them if used as nonspecific adjuvants. Post treated 175 patients with an "autogenous streptococcal toxin" (filtrate); 83 per cent were improved.

Most of these reports are subject to the criticism of Jordan: No satisfactory control of vaccines from the standpoint of laboratory tests and pathologic modification has been reported. Most workers fail to report any controls and treat patients so long that natural remissions have time to occur. It may be justifiable to use vaccines in selected cases under close observation but not with the implication of specificity or of certain cure; the use of vaccines in arthritis rests on pure empiricism. Vaccine therapy was considered unreasonable by Okell who found it impossible to believe that streptococci cause atrophic arthritis when they are practically never found in joints or lymph nodes, even in acute stages of the disease. Green streptococci will produce arthritis of animals (experimentally affected) and (rarely) of man but in both cases the arthritis is purulent and bears no resemblance to atrophic arthritis. There is no evidence convincing to Okell that vaccines ever cured any human disease of known bacterial causation. Yet we are asked to believe that by injecting dead bacteria, a method apparently without curative value in any human or animal disease, we can benefit a disease of unknown etiology which may not be microbic at all. The effects of vaccine can be studied only by scientific statistical methods, without the use of which no physician should take it on himself to express an opinion of vaccine or any other therapeutic measure in a disease as subject to fluctuations as is this.

Having achieved no results from intravenous injection of vaccines, Cohen regarded more highly the "antigen treatment" with filtrates of *Streptococcus cardio-arthritidis*. Desensitizing doses were given subcutaneously. Many patients recovered completely (no details given). On similar

principles Gordon [262] used filtrates (autogenous or stock) of streptococci to which patients were skin sensitive, filtrates being detoxified by formalin. Of 100 patients so treated, improvement was marked in 43 per cent, moderate in 26 per cent, slight in 16 per cent, absent in 15 per cent.

[As we have noted previously, streptococcal skin tests are notoriously unreliable. Others have regarded them unsuitable as indexes for selection of vaccine.—Ed.]

Foreign Proteins. These may be of value in chronic cases but may be harmful in seriously acute cases.[151, 282]

Chaulmoogra Oil. The idea behind this therapy was the observation of McIlhenny (1926) that leprous patients treated with chaulmoogra oil seemed exempt from arthritis. Beneficial results from intramuscular injections of the oil into arthritic patients were reported by McIlhenny (1931) and Hebert (1933). Robinson treated 225 patients with arthritis of various types, mostly of the "infectious" (including gonorrheal) and atrophic types. If deformity was not marked the chaulmoogra oil was "very efficacious" (detailed results not given). Focal and general reactions (malaise, slight fever) were produced by the injections. The oil was injected intramuscularly; abscesses, usually sterile, were produced in 11 cases in which unabsorbed oil accumulated between fascial layers.

[It would appear that the reactions were analogous to those from injections of mild foreign protein and the results no better. The latter treatment would seem preferable to one which produced abscesses, even though only in 5 per cent of cases. We would agree with a recent comment concerning this therapy: "It seems suggestive that although seven and five years have elapsed since the publication of their 'preliminary results' neither McIlhenny nor Hebert has seen fit to report further."—Ed.]

Bee Venom. Patients frequently inquire about this; no reports thereon appeared in 1937.

Diets. The rationale of his dietary program was reviewed in detail by Pemberton, who advised the following: Calories—to meet the individual energy requirements; proteins—about 1 gm. of protein per kg. of body weight, or about 15 per cent of the calories needed; carbohydrates—to supply 33 to 50 per cent of calories needed; fats—to supply 50 to 33 per cent of calories; abundant minerals, vitamins. The diet should not become a "routine" and should be only one factor in treatment. To reduce the intake below the minimal maintenance level is not often indicated and then only for brief periods. A reduced diet should not be given to febrile patients or to those fatigued or at work. Haden approved a diet low in carbohydrates, with adequate vitamins and vitamin supplements (wheat germ, yeast, vagex) and abundant proteins. Cmunt noted no beneficial results from the use of a low carbohydrate diet in cases of "chronic rheumatism" and "deforming arthritis" (no details given).

Others insisted that there is no such thing as a specific diet for such patients (Haden, Wyatt) and no need to avoid meats or citrus fruits (Copeman and Tegner). "Anything that will agree with the patient should be permitted freely" (Cohen).

Additional Intestinal Therapy. High colonic irrigations still found support.[126] Pemberton warned against the excessive use of purges or of bran in amounts which may form mechanical irritants. To correct constipation, Phillips' patients were occasionally given magnesium sulfate and nothing but orange juice for 24 hours.

Vitamins. In atrophic arthritis there may be a deficiency of certain vitamins; the serum may be low in vitamins A and C; a deficiency of vitamin B is also probable, according to Race, but has not yet been demonstrated. These deficiencies are common to various rheumatic diseases, are not specific or striking, and their significance is not clear. Vitamin A was prescribed by some (Ishmael and McBride). Vitamin B contains two better known factors (B_1 and B_2), perhaps six others. Some of the symptoms of B_1 avitaminosis (polyneuritis, lymphopenia, excess lactic acid) are absent in atrophic arthritis; others are sometimes present (e.g. reduced glucose tolerance, subnormal temperature, muscle atrophy); but atrophic arthritis obviously is not a B_1 avitaminosis (Race; Steinberg). Some, however, recommended vitamins B_1 and B_2 as adjunct therapy.[342, 657] Some believed the use of vitamin C helpful.[342] The results ascribed to raw vegetable diets are probably from its vitamin C content, according to Abbasy, Harris and Ellmann, rather than from its low sodium chloride content (Hare, 1936). Race adjudged the results of vitamin C therapy so far "abortive."

The working hypothesis behind Reed's (1935) use of massive doses of vitamin D in arthritis is that there may be an obscure disturbance in calcium metabolism which vitamin D somehow "stabilizes." This therapy was not "specific" however. Reed studied the total calcium exchange in arthritics under such treatment: There was no consistency in the changes of blood and urine calcium and phosphorus, in relation to effects of therapy, except that urinary calcium always increased when improvement occurred but the increase later ceased; thereafter bone density increased, suggesting that the decalcified arthritic bones were recalcified. Steck regarded this therapy nonspecific, unrelated to any definite deficiency of vitamin D in arthritis but "a most beneficial adjunct." He studied the mineral metabolism in "arthritis," considering it of no significance to separate atrophic and hypertrophic types. In most of his cases there was a disturbance of calcium metabolism, not evident in blood but evident as an altered balance, sometimes positive, sometimes "irregularly negative" (details not yet reported). Under vitamin D therapy calcium increases, first in blood, then in urine; then blood calcium becomes normal. When urine calcium increases, improvement begins. An even calcium balance ensues; later urinary calcium decreases and a positive balance is established, associated with recalcification of bones and progressive clinical improvement. But other treatment was then added as "physiologic equilibrium cannot be obtained through the mediation of vitamin D alone." From 150,000 to 300,000 units daily were given. Toxic symptoms (nausea, frequent uri-

nation, lassitude, anorexia, polydipsia; in more severe cases vomiting, gastrointestinal pain, diarrhea) occasionally appeared but ceased if administration of the drug was stopped, or was combated by brewers' yeast. Of an unstated number of patients, 75 to 80 per cent were "benefited."

[We are reminded that at a meeting where one speaker after another was reporting improvement of 75 to 80 per cent of arthritic patients treated by diverse methods, the late Dr. Joseph Miller was overheard to say "There it is again—the inevitable 75 per cent!"—Ed.]

The effect of massive doses of vitamin D on 64 dogs and 773 human beings was studied by Steck, Deutsch, Reed and Struck. Human beings and dogs generally tolerated 20,000 units per kg. per day indefinitely without toxicity. Hypervitaminosis D produced cell injury first; then deposits of calcium. The process was reversible and reparable if administration of the drug was stopped promptly. Intoxication for short periods did not produce demonstrable permanent injury.

Farley gave ertron to 27 arthritics of either type; usually 200,000 to 300,000 units, in stubborn cases 600,000 units, in one case 1,000,000 units, daily, for unstated periods. Toxicity was seldom seen with doses less than 400,000 units daily. [Some of us have noted toxic reactions to such doses.—Ed.] "In severe cases of atrophic arthritis reduction or disappearance of pain was observed. The x-rays have shown remarkable reparative changes in the joints consisting of filling in of the rarefied regions and reconstruction of cartilage. In severe cases of hypertrophic arthritis, granular resorption of exostoses, particularly on vertebrae, and reconstruction of cartilage takes place. Not a single one of this group has failed to respond in some degree to the high vitamin D therapy." Blood calcium and phosphorus remained normal in all but two cases; sedimentation rates dropped. However, high vitamin diets were used, and in severe cases hyperpyrexia also.

[In view of our own experiences and that of others, inciuding those who originated this therapy, it is difficult to understand how vitamin D can have two diametrically opposed actions and fill in rarefied areas of bone in one region and resorb bony exostoses in another. How can it restore damaged cartilage in atrophic and hypertrophic arthritis? Pathologic evidence was not offered and the author's interpretation of his published roentgenograms seems erroneous to us.—Ed.]

Others condemned the use of massive doses of vitamin D as dangerous and as being without a theoretical or practical basis.[126, 342] Some, who considered the treatment "overdone," noted "disastrous results" in acute cases and increased pain and heat even in chronic cases in which 100,000 units were given daily (Ishmael and McBride). However, the usual small doses were recommended as tonics.

There are several preparations of concentrated vitamin D, including viosterol, calciferol, drisdol, Con-Dol and ertron. The use of all of these preparations for arthritis was inferentially frowned on by the Council of Pharmacy and Chemistry[158] which would not accept Con-Dol and Ertron for "New and Non-Official Remedies." On investigation the Council

found no definite evidence that the doses used were nontoxic or effective. They found no scientific evidence to support the claims made and deprecated the unwarranted exploitation of these products by certain manufacturers. [The report of Abrams and Bauer, just published, concludes that the use of massive doses of vitamin D in atrophic arthritis is of "little or no value."—Ed.]

Miscellaneous Medicines and Other Substances. Laymen are likely to think that no cure can be complete without its bottle.[661] However, in atrophic arthritis medicines are of little value. As one writer[29] put it: "Of the hundreds of heralded cures and reliefs with which the pharmaceutic houses flood the literature and our offices I have yet to see one live up to its promises." Nevertheless the arthritic, with his broken morale, can gain new confidence from the judicious use of simple analgesics.[342, 374] The continued use of certain drugs listed by Archer and Discombe may be toxic to some persons. Certain drugs may promote the formation of compounds with hemoglobin, decreasing its oxygen-carrying power: These include the aniline derivatives, such as phenacetin, acetanilid and certain acetylsalicylic acid compounds. Sulfonal, trional and tetranol occasionally produce sulfhemoglobin. Some drugs may cause the disappearance of granular cells of the blood: e.g., pyramidon, allonal, cibalgin, novalgin. The occasional toxicity of phenylcinchoninic acid derivatives is well known. Few patients are susceptible to salicylates or acetylsalicylic acid (aspirin). The perfect form of aspirin, according to one writer,[169] was a stabilized calcium aspirin. The relative merits of aspirin, calcium gluconate-aspirin and calcium phosphate-aspirin were evaluated by Serby and Sideman. For 46 patients with various types of arthritis (six atrophic, 35 hypertrophic, five others) all three drugs were equally analgesic but calcium gluconate-aspirin seemed to produce fewer and milder symptoms in gastrointestinal and circulatory systems.

The "most valuable" of all drugs to Haden was arsenic, used routinely in the form of neoarsphenamine. The intravenous use of ammonium ortho-iodoxybenzoate (Young and Youmans, 1926) fell into disrepute because of occasional serious toxicity; oral compounds presumably were helpful (Smith 1927, Cottrell 1927). Cohen considered the small doses used by others of little value and recommended calcium ortho-iodoxybenzoate (oxoate B), 1.5 to 6 gm. daily; av. 3 gm. The higher doses, although not tolerated by 24 per cent of 125 patients with atrophic arthritis, were more effective: 4 per cent were "cured"; 33 per cent, much improved; 17 per cent, improved; 22 per cent, unimproved.

[Benzoates of one sort or another frequently have been hailed, later abandoned, for arthritis. The newest one is "arthranol," recently given wide publicity in a lay magazine but condemned in the *Journal of the American Medical Association*.[206] —Ed.]

A bizarre and daring procedure was described by Wilms. Having thereby treated malignant syphilis one thousand times without a death, he agreed to give it to a woman aged 65 with "chronic rheumatism" who re-

quested it. For two years the patient had had swollen knees and ankles; painful hips, spine and elbows, and anterior crural and sciatic "neuritis." Treatment consisted of giving "lethal doses of mercuric chloride per os antidoted in five hours with calcium sulphid intravenously grain for grain of the mercuric chloride." A protocol of the patient's immediate reactions is given. Treatment was begun at 11 a.m.: "All pain had left her about 2:00 p.m." It was stated that the procedure could be repeated if necessary several times, with several weeks between treatments. With candor Wilms wrote, "The theory of action of the procedure had better be let alone for the present; there are a few things to think about."

[Especially do we agree to the last part of his quotation. This is apparently the first patient with arthritis he has so treated. No statement as to the patient's condition after the second day was given. Data given are inadequate for one to determine what type of chronic rheumatism she had. In the hands of anyone not familiar with this procedure death might well result.—Ed.]

[Every few months some new drug is exploited for arthritis so assiduously either by unfortunate newspaper publicity or by zealous commercial interests that most physicians at once become suspicious of them regardless of their merit or lack of merit. But arthritic patients soon hear of such drugs and pester their physicians for advice and information thereon. The latter is often difficult to find since the drugs are rarely recommended in the more widely read journals. We shall, therefore, occasionally refer to certain articles in obscure journals so that physicians who wish may read them, we hope with a properly critical attitude.—Ed.]

Causalin (amino-dimethyl-pyrazolon-quinoline-sulphonate) was used for "rheumatism" by Latzel (1927, 1928) in Germany. Two current American reports are noted. One writer [631] treated an unstated number of patients with atrophic and hypertrophic arthritis "which are related conditions, not distinctive diseases," and concluded, "after a four months' study," that results were "promising." Brief abstracts of four cases were given but no other details. Another physician [565] combined causalin with washing of the bowel and hyperpyrexia: 62 patients were treated, exemplifying atrophic, hypertrophic and gonorrheal arthritis, synovitis, fibrositis, and sciatica, even one patient with "secondary hypertrophic osteo-arthropathy" with pulmonary moniliasis (from data given we cannot accept the last diagnosis). Results were "remarkable improvement" in 84 per cent, partial improvement in 11 per cent, none in 5 per cent. Causalin is just another name for causyth. In 1930 the Council on Pharmacy and Chemistry of the American Medical Association condemned causyth as "therapeutically worthless and ineffective except for possible shock effects which might be dangerous." Causalin has likewise been condemned by the Council [159] as a mixture without originality or rationality, "an unsafe and dangerous product" (among other things it contains aminopyrine).

Last year "subenon" was first brought to the attention of the profession via the lay press and was quickly investigated (and condemned) by the Bureau of Investigation of the American Medical Association.[172, 203] "Subenon" (Seydel Chem. Co.) is the calcium double salt of benzoic and

benzyl succinic acid. Over a period of two years 200 patients with atrophic and hypertrophic arthritis were treated.[410] With the idea that arthritis is related to intestinal derangements the drug was used (in 60 cases with other remedies) as an intestinal detoxifier. Results were excellent in 5 per cent, good in 27 per cent, moderate in 30 per cent, slight or absent in 38 per cent. "No mention of control cases has been made. It is my opinion in the face of unlimited references that all cases treated in other ways could be considered control cases, and I did not deem it necessary to repeat such clinical experiences." [410] [The American Medical Association [172, 203] has again called claims made for subenon "ridiculously optimistic."—Ed.]

Sulfur. Since his previous reports on 250 patients with "arthritis" Woldenberg has treated 106 more. In 82 per cent of these 356 cases (types not definitely stated) patients were "free from pain after the sixth injection." Colloidal "sulphur-diasporal" was given intravenously rather than intragluteally as before. "Arthritis" was considered "a metabolic disorder superimposed by infection."

Having observed most of Wheeldon's cases (1935), Clark stated that best results were obtained by giving, in cases of "hypertrophic and mixed arthritis," colloidal sulfur (sulicosol) intravenously in large doses (*total* dosage 360 to 1060 mg., av. 600 mg.; average weekly dose 126 mg.). Of Clark's own 20 patients (representing hypertrophic and mixed types) seven were subjectively, all were objectively, improved. In six years Wheeldon treated with sulfur more than 1500 patients with "arthritis." He developed a "new sulfur preparation," given intravenously, supplemented by the oral use of an "adrenal cortex" (both preparations undescribed). The adrenal cortex presumably improved the patients' sulfur reserves when given alone but even more when used with colloidal sulfur (no data given). Results were not analyzed statistically but were "romantic."

After four years' work with colloidal sulfur Hamilton seemed to damn it with faint praise; the best he could say for it was that he was "favorably impressed." Parmenter gave sulfur baths and sulfur orally to 47 patients with atrophic arthritis: Results were "satisfactory" in 64 per cent of cases; relief was incomplete in 28 per cent, absent in 8 per cent.

[Many of us have used various sulfur preparations, colloidal and otherwise, and have abandoned them as worthless. It would seem easy to confirm statements that 80 per cent or so patients can be promptly freed of pain. We simply cannot confirm this and note few converts to this therapy. Practically all who write on it neglect even to diagnose the types of "arthritis" treated, to study controls or to be critically scientific. Just recently the Council on Pharmacy and Chemistry [160] made a detailed and very unfavorable report on the use of colloidal sulfur for arthritis.—Ed.]

Gold. The curve of acceptance of most "new" treatments for arthritis that are destined to be discarded, rises rather rapidly, reaches its peak in about three to five years, then falls as adverse reports begin to outnumber the optimistic ones. Finally, use of the treatment in any significant degree dies out after about 8 to 10 years. As one physician advised, "make haste

to use a new remedy before it is too late." [714] Unfortunately they are, like the cat, possessed of nine lives and usually linger on too, too indefinitely, as some laggard "researcher" thinks he has discovered their supposed merits and keeps them going, with the help of the commercial houses. American physicians, aware of the supposed value of gold for arthritis but concerned about its toxicity, have been slow to use it, expecting it would die out or be made safer. It therefore seems significant that the curve of acceptance of chrysotherapy is still rising after 10 years of use. At the recent International Conferences at Oxford and Bath gold was the subject of many informal conversations. Two of us (F. C. H. and P. S. H.) were impressed by the restrained yet sustained enthusiasm for this therapy expressed by numerous British and continental physicians of long experience and unquestioned ability, and in England not only by rheumatologists but also by professors of medicine not primarily interested in rheumatism. Current reports on chrysotherapy for arthritis continue to call it, "the medicament of choice in early cases" (Copeman and Tegner), "very impressive though far from miraculous" (Parr and Shipton), "the best means of combatting the disease" (Sashin and Spanbock), "of undoubted value, the best single form of treatment" (Hartfall, Garland and Goldie).

[In view of this, but without meaning to lend our personal approval to it as yet, we shall again review current reports in some detail. Most of us have not used it extensively. The preliminary American report of Snyder, Lust, Traeger and Kelly may be consulted and that of one of us, A. J. K., will shortly appear. In the meantime the report of Hartfall, Garland and Goldie should be "required reading" for those who plan to use this treatment.—Ed.]

Some of the gold compounds used were:

Allochrysin—auro-thio-propanol sulphonate of sodium
Crisalbine—gold sodium thiosulfate
Lopion—auro-allyl-thio-urea benzoate of sodium
Myochrysine (myocrisin)—auro-thio-malate of sodium
Sanocrysin—double thiosulfate of gold and sodium
Solganol B—auro-thio glucose
Triphal—sodium auro-thio-benzimid-azole carboxylic acid

Five reports appeared (two British, one Irish, one Australian, one American) all attesting to the value of chrysotherapy for atrophic arthritis. The least significant report was that of Crawford who gave other forms of treatment with the gold [type of gold used not stated definitely.—Ed.] Of 13 patients three (23 per cent) were "cured," five (38 per cent) very much improved, four (31 per cent) improved, one (8 per cent) relapsed. Sashin and Spanbock treated 22 patients: 12 (54 per cent) were markedly improved, five (23 per cent) slightly improved and five (23 per cent) unimproved. Six months later two patients had had slight relapses, promptly relieved by another course of gold sodium thiosulfate. Copeman and Tegner treated 51 patients (46 with atrophic arthritis, three with ankylosing spondy-

litis, two with "periarthritis") with allochrysin. There was "great improvement or cure" in 58 per cent, improvement in 36 per cent, no improvement in the three cases of spondylitis (6 per cent). The majority received one course; several, two courses. Parr and Shipton treated 70 patients with atrophic arthritis by means of myocrisin: 7 per cent were cured, 50 per cent greatly improved, 13 per cent slightly improved, 10 per cent unchanged, 10 per cent worse; 3 per cent had recurrence; 6 per cent stopped treatment because of reactions, and one patient (1 per cent) died in a toxic reaction.

Following up their series of 1935, Hartfall, Garland and Goldie have made an excellent report of the good and bad results noted in the treatment of 900 patients with arthritis (750 of atrophic type). Their report is so detailed and comprehensive that we cannot here review it completely; all interested in gold therapy should read it. Of the 750 patients with atrophic arthritis treated, 690 completed the treatment. Of these, 10 per cent were cured, 57 per cent markedly improved, 13 per cent moderately improved, 6 per cent slightly improved, 9 per cent unchanged, 2 per cent worse, 3 per cent dead. Follow-up was made in 300 cases. Crisalbine and lopion were given intravenously, solganol B oleosum and myocrisin were given intramuscularly. A careful analysis of relative effectiveness (and toxicity) of each compound revealed that the same number of patients "improved" with each drug, but there were more "cures," and also more toxic reactions, from crisalbine. Preparations given intramuscularly were as toxic as those given intravenously but the former route was easier.

In general, results were better among those who had more than one course and, as one might expect, among those whose arthritis was of shorter duration. Sedimentation rates usually fell during treatment but changes in rate were not always related to results. Some patients improved definitely although their rates fell only slightly or even rose.[296, 521] Of the cases of Copeman and Tegner, rates fell in 69 per cent, continued to rise in 4 per cent, were unchanged in 18 per cent. In 9 per cent the rates rose before they fell; a rising rate after treatment is begun is therefore no prognosis of failure. However, in this series no patient improved whose rate persistently failed to drop. In the cases of Sashin and Spanbock the effect of chrysotherapy on sedimentation rates was notable. Sedimentation rates in the entire group of 22 cases totalled, before treatment, 1051 (av. 48) mm., after treatment, 604 (av. 27) mm. The drop was most evident in 12 patients markedly improved: total rates before treatment, 558 (av. 47) mm., after treatment, 126 (av. 11) mm. Rates of the 10 patients not significantly helped were, total before treatment, 493 (av. 49) mm., after treatment, 478 (av. 48) mm., all rates being after 45 minutes of sedimentation.

Contraindications to chrysotherapy were few: gross renal or hepatic disease, colitis, pregnancy, eczema, severe anemia, a history of previous purpura or agranulocytosis. On the basis of their experiences with toxic reactions Parr and Shipton considered it dangerous to treat arthritic patients with pronounced malnutrition, sweating, cyanosis, tachycardia (the cold, clammy, cyanotic young woman), until

improvement had been effected otherwise; also, to treat patients with edema of feet and ankles.

Plans of dosage varied somewhat but there has been a progressive tendency to use smaller individual and total doses, with several weeks' intermission between courses. Results did not seem entirely dependent on the total amounts given. Copeman and Tegner gave allochrysine intramuscularly every four to seven days: initial dose, 10 mg.; second dose, 20 to 50 mg.; highest individual dose, 100 mg.; total dose for one course, 1 to 1.5 gm. Having had toxic reactions from larger, ascending doses of myocrisin, Parr and Shipton reverted to an initial dose of 10 mg., later doses each 50 mg., no higher, given once a week for 12 doses. Crawford gave 10 mg. of gold at the first dose and again four days later, then every four or five days (schedule—10, 10, 20, 20, 50, 50, 100, 100, 200 and 200 mg.; thereafter every five to seven days 200 mg.; no higher dose). Sashin and Spanbock gave equal doses (5 c.c. gold sodium thiosulphate) once or twice a week intravenously for 25 to 40 injections; if relief was not noted from 25 doses, use of the drug was stopped. Having originally given larger single doses and a total dose of 2 gm. each course, Hartfall, Garland and Goldie strongly urged reduction in individual and total doses: maximal individual dose, 100 mg.; maximal total dose for one course, 1 gm.; injections to be given weekly for about 12 weeks (first dose, 25 mg.; if no pain, second dose 50 mg.; third and subsequent doses, 100 mg. each).

"Every patient should have at least two courses"; this was the opinion of most. Relapses often occur after the first course; less often after two courses. Patients rarely have more than one relapse. With differing plans of dosage the interval between courses varied: four weeks (Parr and Shipton); six to eight weeks (Copeman and Tegner); no less than three months because toxic reactions from the first course may not appear until six weeks after stopping of the treatment (Hartfall, Garland and Goldie; Parr and Shipton). If then the sedimentation rate is still elevated another course should be given.

Toxic reactions were unfortunately frequent though their danger is overestimated according to Copeman and Tegner. Reactions noted by some were not serious: They occurred in 12 (44 per cent) of Crawford's 27 cases: albuminuria in seven, pruritus in nine, rashes in seven, diarrhea in one, stomatitis and "metallic taste" twice each; more than one reaction sometimes occurring in one person. Of the 22 cases of Sashin and Spanbock reactions occurred in four (18 per cent): stomatitis twice, pruritus and urticaria once, pruritus once. Copeman and Tegner noted toxicity in 10 of their 51 cases; reactions were severe in only three cases, and treatment was stopped in only three cases. Reactions were mild: transient dermatitis in two; severe exfoliative dermatitis lasting three months each in two; diarrhea in three; malaise in two; stomatitis and pruritus once; mild albuminuria alone was not considered a cause for stopping treatment. Parr and Shipton noted reactions in 18 (26 per cent) of 70 cases: in 16 of 48 females, but in only two of 22 males; females therefore seemed four times as sensitive as males. There was no relation between age and toxicity. Noted were dermatitis in 10 cases (exfoliative dermatitis in two), affections of mucosae in four, and hemorrhages (uterus, lung, bowel) in five cases. [Since this adds to 19 reactions it is assumed one patient had two types of reaction. —Ed.] The hemorrhages were all among women; one was almost fatal and one was fatal. A young woman died from uncontrollable uterine hemorrhage after receiving 200 mg. as the second dose of her second course, a dose apparently too high for her.

The most comprehensive analysis of toxic reactions, given by Hartfall, Garland and Goldie, deserves close reading. Of their 900 patients treated, trivial reactions occurred in 7 per cent, more significant reactions in 35 per cent, reactions of any kind in 377 cases or 42 per cent. Reactions were slight in 145 (16 per cent), moderate in 178 (20 per cent), severe in 54 (6 per cent) cases. Among the 900 patients, 262 had skin reactions (mostly mild but severe in 28, including five cases of ex-

foliative dermatitis); 75 had stomatitis; 50 had mild enteritis; 85 had jaundice; nine had purpura, one each had agranulocytosis, hypochromic anemia and macrocytic anemia. [Apparently some patients gave multiple signs of toxicity as this totals to 484 reactions in presumably 377 cases.—Ed.] Toxic reactions were more frequent in the first course, less frequent thereafter, but some escaped reactions in the first course, to get them in later courses. When toxicity was apparent, administration of the drug was stopped for two months but a common toxic reaction was not considered a contraindication to further treatment later. According to some,[521] in the order of decreasing toxicity were triphal, sanocrysin, solganol and lopion. Preparations used by Hartfall, Garland and Goldie were equally productive of severe toxicity but crisalbine produced more of the less severe reactions (and more cures). The gold content of any preparation was not the chief factor in determining toxicity; chemical composition seemed more important.

Jaundice, presumably of the catarrhal type, from toxic hepatitis, affected 85 patients; it was slight in 22, moderate in 50, severe in 13 (fatal in two). Curiously, jaundice did not develop in any of the first 100 cases of these workers. The condition, when it occurred, may have arisen in part from an epidemic of "infective hepatic jaundice" which occurred in the region. No ameliorating effect from jaundice was noted in any case.

[Serum bilirubin values were not noted. A certain intensity (serum bilirubin about 8 to 10 mg. or more per 100 c.c.) is apparently necessary before the ameliorating effect of the common types of jaundice is noted, as one of us (P. S. H.) pointed out in 1933. Mild jaundice should not be expected to provoke the analgesic phenomenon; perhaps even the moderate jaundice was not intense enough. However, it seems right to assume that the jaundice should have been intense enough in the 13 severe cases to provoke the phenomenon if this typpe of jaundice could invoke it. Perhaps this type of jaundice is different from others noted and, no matter how intense, cannot invoke analgesia. However, one of us (P. S. H.) met two British physicians who had noted isolated instances of rapid recovery from arthritis during "gold-jaundice." Further observations on this question, with estimations of serum bilirubin would seem of interest.—Ed.]

Of the patients of Hartfall, Garland and Goldie, 20 died: 10 from natural causes, seven from gold toxicity, three from unknown causes (mortality 0.8 per cent or, if the last three patients are included, 1 per cent). Deaths related to gold were as follows: three from purpura, one from agranulocytosis, two from hepatic necrosis, one from exfoliative dermatitis.

There was no certain way of preventing toxicity; the best way was to use small, properly spaced, doses. Reactions seemed more frequent among ambulatory patients; therefore hospitalization, at least during early doses, seemed advisable.[150] Parr and Shipton suggested that loss of gastric acidity favored reactions: 16 of 48 patients with low, or no, gastric acidity and only two of 22 patients with normal gastric acidity had reactions. Many physicians used liver extracts, calcium, glucose and ascorbic acid routinely but in individual cases these seemed useless to prevent or lessen toxicity. Some were impressed with the possibility that "patch tests" with gold might reveal sensitivity thereto.[296] If patients under treatment developed leukopenia further doses should be given cautiously. Eosinophilia or punctate basophilia, considered by some as signs of impending toxicity, were not noted by others.[150] The treatment of toxic reactions was entirely symptomatic. Use of gold was stopped at once. Liver extracts, sodium thiosulfate, calcium gluconate, ascorbic acid, increased intake of fluids seemed useful to some, useless to others.

In conclusion, Hartfall, Garland and Goldie who used gold alone in the treatment of their 750 patients, stated: "We firmly believe that rheumatoid arthritis if seen in its early stages can be cured by gold, and there are few

if any cases of the disease that cannot be improved." Others [521] concluded that the undoubted benefits from gold make it imperative to find a less toxic product or to learn how to minimize the toxicity of those now used.

Vasodilators: Histamine, Choline. Having observed physiologic reactions therefrom, several workers [65, 446] considered it proved that by iontophoresis, molecules of acetyl-beta-methyl choline could be transmitted into human tissues sufficiently to stimulate the parasympathetics. Boyd, Osborne and Markson treated 15 patients with "chronic infectious arthritis": pain was decreased in five, motion increased in six, fatigue decreased in six; many were not improved. Of 36 patients with "infectious arthritis" treated similarly by Martin and Eaton, 57 per cent were "helped," "some became symptom free." Kling and Sashin considered mecholyl iontophoresis much inferior to that with histamine. A procedure for using the latter at home was developed: of 42 patients, 71 per cent were "cured or improved"; 29 per cent not improved. Young recommended a histamine-containing ointment ("imadyl") for home use by patients: of 16 patients 11 were "markedly improved"; five had little or no improvement.

[Probably these methods provide transient subjective relief but results have not been impressive; no adequate comparison between this and ordinary physiotherapy has been made to our knowledge.—Ed.]

Sulfanilamide. In the early work with the prontosils a few patients with "infectious arthritis" were treated with presumed benefit.[424] Veil (1933) noted marked improvement from prontosil I in a case of "rheumatism" or "polyarthritis." A few patients with "chronic infectious arthritis" treated by Gantenberg and Thimme (1935) were reputedly benefited. "Arthritis deformans" was reported as successfully treated with sulfanilamide by Ory (1936). Mitchell and Trachsler noted the death from agranulocytosis of a child with Still's disease given prontylin (dose and duration unstated). A patient of Brown, Bannick and Habein with an acute exacerbation of chronic atrophic arthritis developed hemolytic streptococcal septicemia; prontosil II and sulfanilamide cured the latter but did not affect the joints. Results in a few cases of atrophic arthritis were "questionable."

[No study on the effects of sulfanilamide in a significant number of cases of atrophic arthritis has yet appeared but one by Bauer and Coggeshall soon will. One of us (P. S. H.) has treated several patients, with disappointing results and with marked toxicity in a few, with severe, nonfatal agranulocytosis in one, and with prolonged fever in two.—Ed.]

Rest and Movement. The problem for arthritics should not be one of "rest *versus* exercise" but "rest *and* exercise" and not too much of either; not so much rest as to permit ankylosis and not so much exercise as to keep up inflammation. Many laymen and physicians believe that joints must be rather constantly moved to prevent ankylosis; for the latter, exercises in bed or a complete range of motion of affected joints a few times

daily will suffice. Complete rest in bed for three to six weeks was advised in early or severe cases when possible; otherwise reduction of as much occupational trauma as possible.[282, 322, 389, 514, 545]

Physical Therapy. Physicians may argue the merits of other forms of therapy but they agree on the value of physical therapy although they may express preference for one or another form. The cost of their disease is so great that patients must be allowed, and instructed, how to use simple methods of *home physical therapy* to supplement professional service; these were described.[282, 545] The indications for, technic, and relative merits of the common forms of physical therapy were given; the importance of correct body mechanics was stressed.[292, 389, 391, 632, 715] For hands and feet, melted paraffin baths are most useful.[545, 661] The biologic action of infrared, luminous and ultraviolet light and their indications were reviewed.[209] The merits of electrotherapy,[392] hydrotherapy[682, 742] and Pistany mud packs[495] were noted.

Arguments on the relative merits of short wave diathermy and of ordinary (long wave) diathermy were continued. Dalton championed the view that short waves have a specific effect unrelated to their heat production, a view rejected by the majority, who believe that claims to superiority of short wave diathermy are mostly fallacious. The main effect of both short and long waves is from heating and no superior or specific action of short waves has been proved.[51, 161, 163, 171, 390] However, short wave therapy has certain technical advantages over long wave diathermy; for the former no direct contact of metal and patient is required, a useful fact in treating tender, inflamed regions. The clinical application of short wave therapy was discussed[336, 553]; it seemed more valuable in atrophic arthritis and fibrositis than in hypertrophic arthritis or sciatica.[355]

The aims and methods of the English spas and the indications for immersion baths, manipulation pool baths, massage douche baths, vapor baths and mud packs were noted (Thomson). In one way or another all the waters promote elimination, "one of the most important factors in the spa treatment of rheumatic diseases." Spa therapy is not practical in acute gout, and is of "very doubtful value" if severe fever accompanies chronic atrophic arthritis.[678] The facilities of a physical therapy clinic for London bus men were described.[661] Although there are more than 8000 mineral springs in the United States, there are only 20 or 30 American spas; these were listed and the work of the Saratoga Spa was described by McClellan. The education of American medical students in physical medicine, including roentgen-rays and radium, is very meager; in 60 accredited medical schools an average total of only five hours is devoted thereto (Lowry). Entrance requirements for the 14 approved American schools for physical therapy technicians were noted.[155] Brown outlined the organization of a teaching clinic for physical therapy. It behooves physicians to learn the general principles of physical therapy so that they can properly prescribe physical treatments for patients rather than to leave the prescription of massage and exercises to

"the gambling instincts of the technician" (Hansson). Criteria by which the Council on Physical Therapy adjudges apparatus or forms of physical therapy for Council acceptance were discussed.[162] The history of physical medicine was briefly outlined by Rolleston.

Occupational Therapy. Whenever possible, occupational therapy should be prescribed as an important part of treatment for arthritic patients (Pattee). It should be closely integrated with physical therapy. Occupational therapists use a variety of methods applicable in all but acute cases. These methods, many of which can be used at home, can do much to restore muscle tone and joint mobility, and to increase the patient's confidence that useful articular function can be regained.

Roentgen-Rays and Radium. Opinions differ as to the value of roentgenotherapy for chronic arthritis (Fineman). A few recent writers have reported an analgesic (but rarely a "curative") effect in hypertrophic, more often than in atrophic, arthritis. Some writers noted some, others no, significant results in atrophic arthritis or spondylitis. Kahlmeter summarized 12 years' experience with roentgenotherapy in 4000 rheumatic cases and gave his plan of treatment for each type. It was much less effective in atrophic arthritis than in other types. Its effect on periarticular inflammation was beneficial; that on intra-articular disease was of "exceedingly slight value"; no significant effect on destroyed cartilage or chronic intra-articular exudates can be expected. Hernaman-Johnson also concluded that roentgenotherapy to individual joints may give some temporary relief but does not affect progress of the disease.

Ingestion of radon in doses of from 80,000 to 240,000 Mache units gave no relief to patients with atrophic arthritis (or with hypertrophic arthritis, fibrositis or neuritis) (Howitt, Pillman-Williams and Russ).

Fever Therapy. Results of fever therapy were not impressive; they were naturally somewhat better in acute and subacute, than in chronic, atrophic arthritis. Most workers concluded that fever therapy should be used only as an adjunct to other therapy; it may provide some temporary analgesia, but recurrences were common.

Of 20 patients with acute rheumatoid arthritis treated by Stecher and Solomon, 12 (60 per cent) received "prompt relief and apparent cure"; eight (40 per cent), partial relief. The course of the disease was "favorably modified in every case." Sessions of fever were each four to five hours at about 105° F.; two to six sessions were given. Bierman's results were also better in acute than in chronic cases. Of 41 patients (acute and chronic), 50 per cent noted some definite and "permanent" improvement. In most of the chronic cases relief was only temporary. Of Shepard's eight patients seven were "definitely improved." Davidson and Warren tried to correlate clinical and roentgenologic improvement of 24 patients with "infectious arthritis" followed one to four years. Each patient received, apparently, only one session of fever (four hours at 40.5° C.) but a "hot bath routine" intermittently thereafter. Results were "failure" in three cases with no clinical or roentgenologic improvement and in six cases with temporary clinical but no roentgenologic improvement (total 38 per cent). In 15 cases there was clinical and roentgenologic improvement (recalcification of subchondral bone; increase in density and number

of bony trabeculae). [Clinical improvement can occur without roentgenologic improvement; indeed, after patients are clinically "cured," certain roentgenographic changes may continue to develop as the pathologic reactions initiated by inflammation "resolve" to their end-stage.—Ed.]

Of Brodribb's eight patients, four were permanently, four only temporarily, improved by fever therapy. Seven patients of Spekter and McBryde and four of Williams, with atrophic arthritis, were only temporarily benefited. But results were much better in 10 cases which Williams called "chronic arthritis." Schnabel and Fetter noted the following: Of 17 chronic cases, little or no improvement in nine, moderate but only temporary improvement in eight. In six acute or subacute cases, notable relief lasted in only two. Simmons used fever as adjunct therapy for 36 patients: 78 per cent were improved; hence, fever therapy was considered valuable.

[So many measures were used that results of any one cannot be evaluated.—Ed.]

Climate. It has not been proved that residence in a warm, dry climate improves a patient's prognosis; if his environmental factors are the same, he may be as well off at home (Miller). In one Boston hospital rheumatic patients noted considerable symptomatic relief when the humidity of their rooms was stabilized by air conditioning.[745]

Sympathectomy. Most writers [606, 716, 717] no longer consider sympathectomy suitable treatment for arthritis. Adson recommended it only when atrophic arthritis is associated with marked annoying vasospastic phenomena. Reviewing reported results, Learmonth concluded that sympathectomy may modify the pain but not the course of the disease and that the variability in its results argues against the view that arthritis is due to impoverished circulation. Corbin performed lumbar sympathectomy on several cats; two years later there were no significant gross or microscopic changes in bones or joints. On other cats both lumbar sympathectomy and lumbar and sacral deafferentation were done; thereafter the deafferented limbs were usually carried in a position of extension and either abduction or adduction. In the next one to three years, arthritic changes like those of malum coxae senilis (degeneration and erosion of cartilage, eburnation, bone hypertrophy, some synovial hyperplasia) developed in deafferented hip joints, changes believed to be due to diminished articular sensibility.

[Could they have resulted from trauma alone; from use of limbs in markedly abnormal positions?—Ed.]

Orthopedic Methods for Prevention and Correction of Deformities. Nonsurgical methods. Correction of deformities too often consists of "the correction of mistakes made by doctor or patient." [322] However, such great strides have been made that even when deformities are present, no longer is the deformed cripple an outcast from the big hospital and doomed to a life of hopeless crippledom.[681] Deformities are generally due to muscle spasm followed by capsular shortening and intra-articular changes. Muscle spasm often can be corrected by simple rest [322, 666]; if this is inadequate, splints or casts can be used. Some preferred to apply one, or a series, of light metal (duralumin) splints or light plaster shells to correct or prevent deformity.[238, 322, 373, 417, 545, 666] Some medical supply houses now put up plaster bandages, in neat packages, ready for instant use. Plaster bandages are es-

pecially useful for wrists, knees and shoulders. If ankylosis is impending, joints should be placed in an optimal position for future function. These positions were again described.[238] The prolonged application of plaster casts fosters deformities; if casts are used they must soon be bivalved.[238] Extension by weights is indicated for certain joints, especially hips.[238] Some[333] considered manipulation of joints under anesthesia generally dangerous; others approved it in suitable cases (with disease not active in any joint). The hazards of postponing manipulation too long may be greater than doing it "too early" when slight inflammatory activity is still present.[238, 322, 681] Methods for correction of body mechanics were again described.[238, 397, 666] The management of painful arthritic feet by nonsurgical means (pads, bars, plastic foot support), and surgical means (tenotomy, metatarsal excision) was outlined.[661, 676] Bohlman recommended aspiration and injection of air into arthritic joints with exudates.

[There is no reason why medical men, especially those who do not have the services of an orthopedic colleague at hand, can't learn the simpler orthopedic procedures.—Ed.]

Surgical methods. General and special requirements of the various surgical procedures for correction of joint deformities were reviewed:[238, 333, 681, 730] The arthritis must (usually) be entirely quiescent for at least six months; the patient's physical and financial condition and morale must be sufficient to permit fulfillment of the (sometimes) long periods necessary for operation and subsequent observation; the expected functional gain must be worth the effort (Wilson). Indications for excision of joints were marked articular destruction and severe pain.[238, 681] Arthrodesis was recommended, especially for painful hips resistant to long treatment.[238] Osteotomy was recommended for joints, especially hips and shoulders, ankylosed in bad positions, or for flexion contractures with damaged joints and narrow joint spaces.[730] Arthroplasty was especially useful for ankylosed elbows, knees and hips.[238, 378, 573] Arthrotomy and lavage with Dakin's solution seemed valuable in resistant subacute arthritis of knees.[238] Removal of loose bodies is sometimes required to correct recurrent "locking."[238] In cases of chronic hyperplastic synovitis with effusion, synovectomy may be valuable.[238, 730] The use of posterior capsulotomy for correcting obstinate flexion deformities of knees, unrelieved by physical therapy, weights or splints, is spreading.[238, 322, 730] Usually this is done only in entirely quiescent cases but Littlefield obtained excellent results, even in the presence of mild clinical activity.

Psychotherapy. The value of psychotherapy as an adjunct to other treatment for arthritis, especially the atrophic type, is being increasingly appreciated. A certain amount of psychotherapy, consciously or unconsciously applied by the attending physician is essential to alleviate the despondency which these diseases engender.[126, 672] By a spirit of continued optimism and friendly encouragement, the physician, the clergyman, the family and friends of an arthritic patient all have their place in restoring the patient's self-confidence.[545]

(*To be continued*)

CASE REPORT

FURTHER EVIDENCE IN REGARD TO FUNCTIONAL BUNDLE-BRANCH BLOCK *

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IT is the purpose of this presentation to add some further evidence in regard to the occurrence of functional bundle-branch block. I shall attempt to do so by a partial review of the literature, the presentation of a case report and consideration of some of the mechanisms which may be responsible for this abnormality. Strictly speaking, the term " functional bundle-branch block " should be restricted to those instances in which there is no organic basis either temporary or permanent for the production of the conduction disturbance. In general, however, the literature has dealt with transient or temporary bundle-branch block and functional bundle-branch block as synonymous terms. Therefore, certain examples of transient bundle-branch block have been included.

The electrocardiograph has added greatly to our knowledge of the heart and the instrument is indeed indispensable in the practice of cardiology today. Cardiologists have been most eager to present the evidence which indicates the value of the instrument. We have, however, been less inclined, perhaps, to elaborate on instances in which the electrocardiogram may, in fact, be misleading because of the imperfection in our knowledge of its interpretation. Some few years ago we considered the so-called coronary T-wave as pathognomonic of coronary closure. Gradually, however, experience has taught us that other conditions may produce similar T-wave changes. We now view the electrocardiographic changes more correctly as only one link in the chain of evidence. In like manner, it has taken time for us to discover the full facts about other electrocardiographic findings. Until very recently it was generally accepted that the electrocardiographic picture of bundle-branch block always carried a very grave prognosis, being always indicative of serious organic heart disease. The fact that one would be right in such an interpretation in the vast majority of instances does not in anyway lessen the tragedy of offering such a prognosis to even one individual for whom it was not correct. We cannot rightly excuse such a mistake on the grounds that we were confronted with an unusual or rare finding. It happens that so far as the individual under consideration is concerned, this " rare " finding is the only one of significance.

REVIEW OF LITERATURE

Even a partial review of the literature indicates that evidence of transient and functional bundle-branch block has been accumulating for many years. As early as 1913, Lewis [1] found a case in which transient bundle-branch block occurred during an acute febrile attack. However, Hermann and Ashman [2] have called

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attention to the fact that the electrocardiographic curves in this case would now be considered highly suggestive of coronary disease. In this instance, therefore, we might readily suspect that temporarily, at least, there was an organic cause for the bundle-branch block. In 1915, Wilson [3] reported a case which would more correctly be termed "functional" bundle-branch block. He states: "The normal rhythm when spontaneously present could be converted into an atrioventricular rhythm with right bundle-branch block by indirect or direct stimulation of the vagus nerve, and the abnormal rhythm, when spontaneously present, could be converted into the normal rhythm, by the administration of atropine in doses sufficiently large to paralyze the vagi." Robinson [4] in 1916 reported a case in which the defective intraventricular conduction was clearly not based on pathologic lesions. He advanced the theory that the interference with conduction was due to "functional fatigue." Willius and Keith [5] in 1927 cited three cases of intermittent bundle-branch block. Each had evidence of myocardial disease. The authors explained the conduction disturbance on the basis of myocardial fatigue. In two of the three cases the disturbance was present only during cardiac failure. Baker [6] in 1930 reported a case in which bundle-branch block appeared whenever the cardiac rate was high and disappeared when the rate decreased. He interprets this to mean that the reduction in duration of the cardiac rest period, accompanying the increased rate, caused the intracardiac circulation to become temporarily inadequate to maintain the normal functioning of the bundle of His. Anoxemia of the conducting tissues was therefore the mechanism responsible for the conduction defect. In proof of this it was observed that during artificial administration of oxygen an increase in heart rate did not cause bundle-branch block. Baker cites, also, the fact that Lewis and Resnik had previously demonstrated that in some instances simple asphyxia affects the intraventricular conduction, and that others had observed bundle-branch block to diminish in degree following the administration of oxygen.

In 1930, Wolff, Parkinson and White [7] made a most important contribution when they reported a series of 11 cases in which they observed bundle-branch block and short P–R intervals in healthy young people who were prone to have paroxysmal tachycardia. It was observed in several of these cases that whenever the P–R interval increased spontaneously to normal, or in response to exercise became normal, then the bundle-branch block configuration disappeared. Likewise, in one instance (Case 1) the administration of atropine restored the complexes to normal and increased the P–R interval from 0.1 second to 0.15 second. The authors interpreted their findings as indicating that a strong vagal influence was responsible for the displacement of the normal pacemaker in the auricle and also for inhibition of one branch of the bundle of His with resulting bundle-branch block. In 1933 Wolferth and Wood,[8] noting that complexes such as those described by Wolff, Parkinson and White are observed once in every one thousand electrocardiographic examinations, sought to explain the mechanism on the hypothesis of an accessory pathway of auriculo-ventricular conduction such as was described by Kent [9] between the right auricle and right ventricle. This hypothesis has received, however, very little support.

Hermann and Ashman [2] in 1931 reviewed the cases of transient bundle-branch block that had appeared up to that date and presented eight cases of their own. They emphasized the fact that in most of the presented cases the transi-

tion from normal conduction to defective intraventricular conduction has been a gradual process, and in most of these myocardial exhaustion and anoxemia, functional fatigue, the accumulation of products of cell metabolism and congestive heart failure were precipitating causes. In three of their own cases, however, the transition from the normal electrocardiogram to that of bundle-branch block occurred abruptly. These three cases are of particular interest. In Case 1, indirect vagus stimulation by deep inspiration would cause a sudden change from bundle-branch block to normal curves. It was observed also that coincidentally the heart rate always decreased from about 75 to 65 beats per minute. Also curves taken after prolonged rest showed normal conduction, whereas slight exertion caused the bundle-branch block configuration to reappear. Although it was not stated that this patient had definite organic heart disease, it seems most likely that anoxemia of the conducting tissue or " functional fatigue " caused the block, and that the improvement observed following vagus stimulation was due to the " slowing of the heart rate," with consequent relief of the anoxemia. In the other two cases definite organic heart disease was present. In Case 2, after slight exertion, normal complexes could be produced by indirect vagus stimulation, although the heart rate altered little. Here again, the relief of bundle-branch block by rest in bed indicates the effect of " functional fatigue." In Case 3, also, periods of normal conduction were observed to follow prolonged rest.

In 1932, Elliott and Nuzum [10] reported a case of unusual interest. Their patient's electrocardiogram showed a predominant bundle-branch block configuration. There were a few normal appearing complexes. During a short period of two to one auriculo-ventricular block when the ventricular rate was markedly slow the bundle-branch block disappeared. As soon, however, as the auriculo-ventricular block disappeared and the ventricular rate increased to normal, there was a return of bundle-branch block. In response to vagus stimulation, the auricular rate could be slowed, and the bundle-branch block configuration again disappeared. In 1932, also, Morris and McGuire [11] reported two patients in whom cardiac symptoms came on acutely and in whom the electrocardiogram demonstrated transient bundle-branch block. In the first of these cases acute pulmonary edema and a state of shock were present at the time the bundle-branch block curves were taken. In the second case, likewise, there was a state of collapse with very low blood pressure during the time that bundle-branch block was demonstrated. These cases, then, like that of Baker, were presumably due to temporary inadequacy of the intracardiac circulation to the bundle of His. Carr [12] in 1933 also reported transient bundle-branch block which accompanied an acute cardiac incompetency. In 1934 Willius and Anderson [13] reported a case of transient recurrent bundle-branch block. Complexes with normal conduction were often followed in 24 hours by those showing bundle-branch block, although, clinically, the patient was unchanged. Their patient was a hypertensive and also in the age group where coronary disease is common and, therefore, they explain the phenomenon on the basis of transient recurrent disturbance in the circulation, affecting the bundle.

Tung [14] in 1936 reported two additional cases of the type previously described by Wolff, Parkinson and White. Two healthy young Chinese, who were subject to attacks of paroxysmal tachycardia, presented between attacks electrocardiograms characteristic of bundle-branch block with a short P–R interval.

He also had observed, but did not report in detail, three other individuals whose electrocardiograms presented a similar characteristic, but who were not subject to paroxysmal tachycardia. In Case 1 of his report, administration of one milligram of atropine caused a gradual reversion to normal ventricular complexes with a normal axis, although the P–R interval continued short. In the second case, atropine (2 milligrams) had no effect. Kurtz [15] in 1936 reported six cases of transient bundle-branch block. In each case, there was, however, advanced organic heart disease. He felt that the block was due to disturbance of circulation and nutrition of the conduction tissue.

Case Report

Mr. J. W. B., aged 59 years, was first seen on April 24, 1936, complaining of recurrent attacks of palpitation of six years' duration.

His family history was negative except for tuberculosis in his mother, who died at the age of 60 years. There was no history of cardiovascular disease in the family.

He had worked as a furniture salesman for 38 years, traveling a rather wide territory. He denied all previous illness except arthritis of the shoulders, which was relieved in 1929, by extraction of his teeth. In 1934, an automobile accident resulted in fracture of the body of the fourth lumbar vertebra with consequent deformity and slight disability.

He stated that in 1930, for the first time, he had an attack of palpitation, which was sudden in onset, lasted one hour and ended abruptly following an injection by his physician. In 1933, another attack of the same character lasted about three hours and subsided without medical treatment. From that date until one week prior to my first observation he had several attacks of very short duration that required no treatment. Between attacks he was entirely free of all cardiorespiratory symptoms and worked quite hard. His last attack occurred one week prior to the present examination. He awakened one morning with a sense of palpitation, smothering, weakness and apprehension. The former was so severe that he called a physician, who gave him a hypodermic. The attack ended abruptly some five or six hours after onset.

Physical examination showed an elderly man, whose development and nutrition were good. His temperature, pulse and respirations were normal. The findings of importance were as follows: There was moderate retinal arteriosclerosis. The thyroid was not enlarged and there were no abnormal masses in the neck. There was likewise no abnormal pulsation or venous engorgement in the neck. The lungs were normal throughout. The cardiac impulse was not seen or felt. Percussion showed the heart not to be enlarged. The heart sounds were of normal character and no murmurs were present. The heart rate was 70, the rhythm regular. Blood pressure was 128 systolic and 80 diastolic. The abdomen was negative. The extremities were likewise negative. The diagnosis was paroxysmal auricular tachycardia.

The electrocardiogram in the three standard leads (figure 1) showed relatively low amplitude of the Q.R.S. complex, the maximum being six millimeters in Lead I. There was a left axis deviation and the P–R interval was 0.18 second. The Q.R.S. interval was 0.08 second. Being much interested in the carotid sinus reflex, I decided to test its effect on this patient. All tests of carotid pressure were made in Standard Lead II. Pressure on the right carotid (figure 2) did not change the form of the ventricular complexes nor alter the P–R interval. However, there was marked slowing of the heart, the R–R interval increasing from 0.9 second to 1.12 second. With subsidence of the effect, the rate slowly increased and the R–R interval became 1.04 seconds. Following left carotid pressure two different types of response were obtained (figure 2). On the first trial there was complete inhibition of the ventricles

for a period of six seconds. There was marked slowing also of the auricle, the P–P interval increasing gradually from 0.9 second before carotid pressure to a maximum of 1.26 seconds during carotid pressure. As the reflex subsided the ventricular complexes returned and followed the P-wave normally. The second attempt with left carotid pressure (figure 2) produced results at first similar to those following right carotid pressure, but after the pressure was continued for 4.6 seconds the ventricular

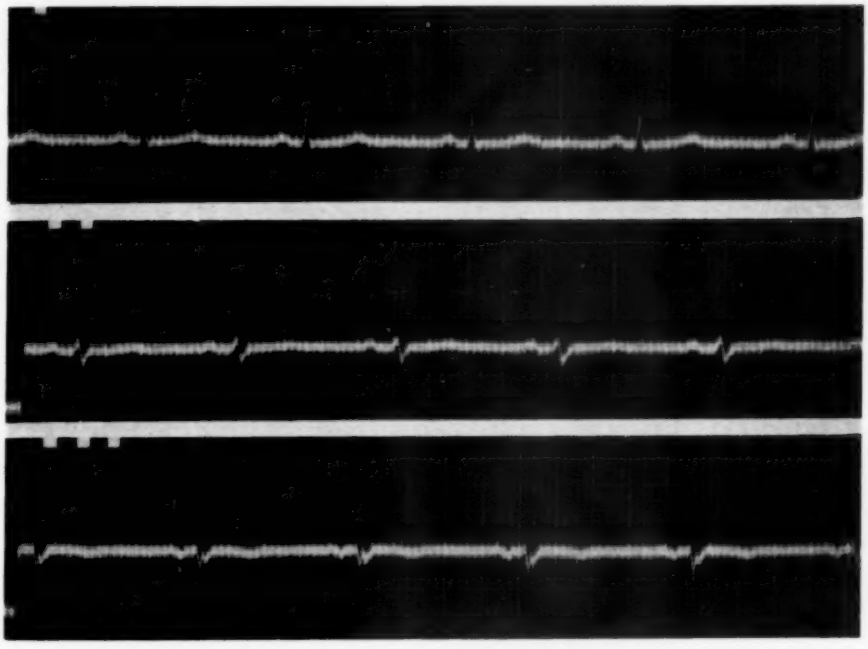

FIG. 1. Three standard leads.

complexes suddenly took on the characteristics of bundle-branch block, which were maintained for three heart cycles, the complexes being exactly equally spaced and at intervals of 1.4 seconds. There was then an abrupt return to normal complexes. The patient had experienced slight dizziness during both tests of left carotid pressure but subsequently felt entirely normal. He has continued well and required no treatment.

DISCUSSION

There is no doubt that we have sufficient evidence to the effect that bundle-branch block may be due to causes other than serious heart disease and also that it may be a transient or functional phenomenon. The literature indicates three chief possible mechanisms for such phenomena. First, bundle-branch block may be due to " functional fatigue." In such instances, the intracardiac circulation to the bundle of His is inadequate and it appears that progressive myocardial exhaustion and anoxemia, accumulation of products of cell metabolism and congestive failure are the cause of the bundle-branch block. Most of the cases observed in the literature have fallen clearly under this grouping. In such cases

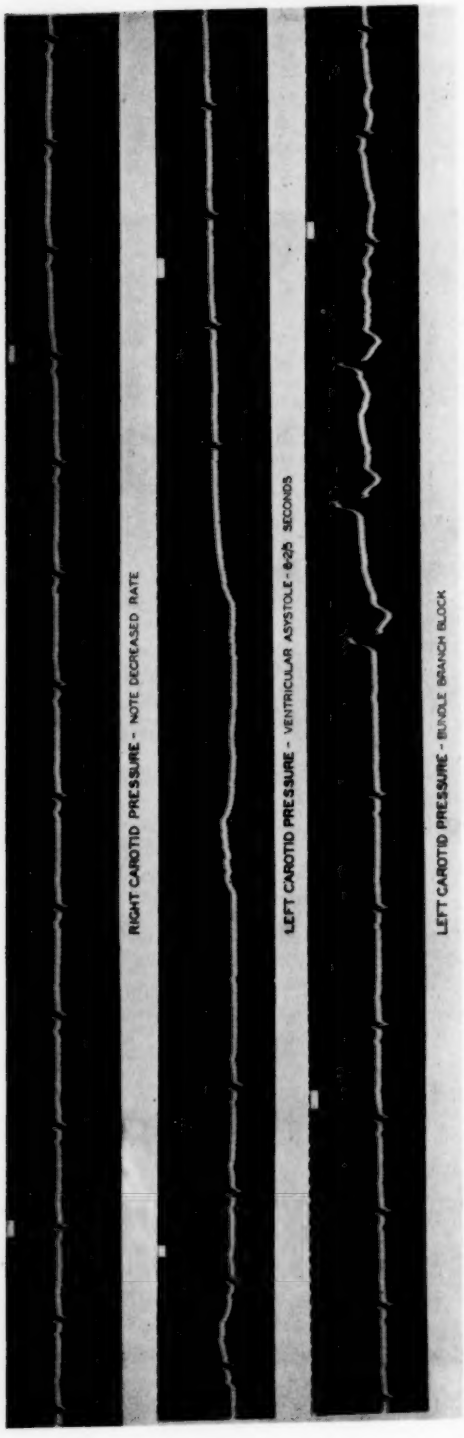
RIGHT CAROTID PRESSURE - NOTE DECREASED RATE
LEFT CAROTID PRESSURE - VENTRICULAR ASYSTOLE - 0.25 SECONDS
LEFT CAROTID PRESSURE - BUNDLE BRANCH BLOCK

FIG. 2. All tracings in Lead II. The lead marker indicates beginning and end of all carotid pressures.

there is definite and usually serious heart disease, but periods of normal conduction may occur as the intracardiac circulation through the bundle improves as the heart rate is slowed by various methods, such as rest, medication or vagus stimulation. Second, it appears possible from studies of comparative anatomy that curves suggesting bundle-branch block may be due to abnormally rapid conduction of the cardiac impulse from right auricle to right ventricle by way of an accessory bundle of conductive tissue, the bundle of Kent. There has, as yet, been no demonstration of this pathology in a case which presented the abnormal electrocardiogram and, in fact, the proponents of this hypothesis admit that they have no direct proof of it.

Third, it is apparent that bundle-branch block may be due to increased vagus effect. This would seem to be the logical explanation for a number of cases which are observed in the literature, particularly those of Wolff, Parkinson and White, and also is the means of explaining the findings in the case here reported. In this case we clearly have evidence of a highly-active carotid sinus reflex which, in one instance, caused complete inhibition of the ventricle and later manifest its inhibition unequally on the two main divisions of the bundle, thereby causing bundle-branch block. The vagus effect here was clearly one of direct action on the conducting tissue and not due to any alteration in heart rate. It is apparent that in those instances of bundle-branch block due to functional fatigue, vagus stimulation may relieve the block by means of slowing the heart rate and improving the circulation to the bundle, whereas, in another instance, vagus effect may be the cause of bundle-branch block because this effect is manifest unequally on the two divisions of the bundle of His.

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EDITORIAL

A RESEARCH CLEARING HOUSE IN THE MEDICAL SCIENCES

Medical research has not often been benefited by ideas picked up from literary scholarship, but an excellent one is now knocking at our door. It can be seen in practical form in a publication, edited by James M. Osborn, formerly at Oxford but now at Yale, and issued by the Modern Humanities Research Association. This is an international organization for the advancement of literary research, with headquarters at Oxford. Called *Work In Progress*, their publication lists over two thousand separate projects now in the hands of literary scholars.

The purpose of their publication is to serve as a clearing house, making it possible for research workers all over the world to know what other researchers are doing. The success of the Editor in gathering information is demonstrated on every page by the wide range of universities whose work is reported. To select an example at random, the following distribution is observed on a single page from the section on French literature of the nineteenth century: Yale, Aix-en-Provence, London, Rome, Pecs (Hungary), Ohio State, Bryn Mawr, Budapest, Wisconsin, Pennsylvania, Strasbourg, Griefswald, Genoa, Lille and Harvard. Only through the medium of a clearing house can these workers in common or related fields be known to each other.

Medical research is being carried on in even more widely flung centers. Again and again medical history has demonstrated that important discoveries have no regard for geography. No one institution or single country can afford to disregard parallel investigations being carried on elsewhere, for there can be no isolation in medicine. A clearing house for medical research is, therefore, long overdue.

Three principal functions should be visualized for an agency of this kind. The first has already been touched on: To serve as a means of making known to each other, research workers of similar interests so that they can communicate whenever it may be desirable. For example, M. Blanc in Paris may have been experimenting with the host function of the cockroach at the same time Dr. Green in St. Louis may be seeking to establish a connection between cockroaches and influenza, and in Buenos Aires Dr. Roya may be observing the same insect in connection with cancer research. Obviously some simple, dependable, up-to-date and accessible method is needed to help these men to exchange information if they so desire. Few discoveries of any magnitude or importance have been completed without obligations to other minds. Furthermore as specialization increases an early exchange of ideas becomes imperative.

The second function of such a clearing house is to expose 'non-purposive' duplication where it already exists, and diminish its frequency in the future. Every veteran of the laboratory is familiar with examples of the gross wastage caused by such duplication. There are some occasions, quite naturally, when such duplication is justifiable and even desirable, provided it is undertaken deliberately and with the knowledge of those directly concerned. But blind duplication, of which there have been many unfortunate instances is inexcusable in this era of efficiency. Moreover at a time when research grants are tending to diminish it is especially important to use every dollar wisely. Money employed in duplicated research is too often money wasted.

The third function of the proposed clearing house should be directed toward the allocation of certain lines of research so that there will be as few blind spots as possible in a research program. It is very easy and tempting, as most investigators will attest, to be led off on a tangent and ultimately to abandon the original concept. But by a prearranged plan aimed at dovetailing research results so that when completed the sum of all the parts will equal the whole, much lost motion, money and time will be prevented. In this respect medical science could learn much from research methods used by the General Motor's Research Corporation under the directorship of Doctor Kettering. Several years ago, this greatest of engineers told me about a method he was then using in the study of combustion in motor engines, a program which on first thought seems far afield from mechanistic discovery. Thousands of corn seeds were planted. Every day as growth progressed the oxidative reactions of germination were critically studied. At the end of each week experts in physics, chemistry, biology and engineering met the combustion investigators and offered suggestions and criticisms of their work. By this plan the researchers were kept in the straight and narrow way of their quest and much waste of time and effort was avoided by not studying remotely related, though interesting side reactions. If such a method were adopted in planning a cancer research program the solving of the cancer enigma might be greatly accelerated.

In urging these considerations I have based my arguments on the practical necessity of conserving time, money and energy. But as scientists we must not overlook the fundamental fact that most of our advances have been due to the application of an orderly plan of work, what we refer to as *the scientific method.* This method begins with careful observations, proceeds by checking the conclusions with experiments, and then pours the tabulated experience into the great common fund of knowledge from which we draw as required. The public calls this fund of facts "science," but we know that science is not a body of knowledge, but the method by which facts can be established. The last important extension of the scientific method was the development of systematic bibliography, which enables a researcher, who wishes to pursue a specialized subject, to place his fingers immediately on material already written on that subject.

And now the scientific method is ready for the next step, which is to utilize a clearing house that will enable researchers, if they so desire, to communicate with others *before publication.* Knowing what *has been done* is not enough; communication should be made possible while an experiment is under contemplation or in progress.

The details of organizing a clearing house to serve medical research can be easily worked out. Each country could have a subsidiary clearing house but a 'medical generalissimo' with a central clearing house should be the research director-in-chief. In their publication, *Work In Progress,* the literary people have decided on the printed list, which for their purpose is cheaper and more useful than a central bureau where card files and other records are maintained. For medicine a combination of both procedures might be desirable, a central office with a medically trained director who would also edit an annual list of *Medical Research in Progress.* The cost of its maintenance, a few thousand dollars, would be paltry indeed compared to the benefits it could bring about. One point which would have to be threshed out in advance is the extent to which this clearing house would serve as a "register," or device for staking out claims to areas of research. In principle, there should be no monopolies in medicine, no one should have prior right to any cure or technic where life and death are involved. Yet there may be instances where a research worker deserves some protection until his discoveries are ready to be announced. In these exceptional cases no report would appear in the published list or some procedure could be developed similar to the "preliminary reports" which are now found in medical journals. Details such as these can readily be worked out.

In connection with the above discussion it is very interesting to note that a National Council on medical education, licensure and hospitals, to serve as a "central clearing house" for existing groups concerned with the educational needs of American medicine, has been recently proposed by Dean Willard C. Rappleye of the College of Physicians and Surgeons at Columbia University.

Practical considerations demand, and scientific method requires that some kind of research clearing house be established. Great medical problems are yet unsolved, valuable human lives go prematurely over the precipice and we must have every tool easily available, which will help us in our work.

C. W. Lieb

REVIEWS

The Endocrines in Obstetrics and Gynecology. By RAPHAEL KURZROK, Ph.D., M.D. 488 pages; 23.5 × 15 cm. The Williams and Wilkins Company, Baltimore. 1937. Price, $7.50.

It is gratifying that the author has covered these constantly changing subjects with an open mind, and that he calls attention to those phases in which much work yet remains to be done. This book, therefore, as well as any other book dealing with endocrinology, is not the final word, nor does the author claim it to be.

There are 30 chapters with an excellent bibliography appended to each. There follows an author and subject index. The book is in pleasing form with clear type. Numerous excellent microphotographs illuminate the text, while the graphic charts serve to illustrate the data.

After fundamental chapters on embryology, histology, physiology, and chemistry, there are chapters devoted to a detailed consideration of each of the hormones. The author then discusses such important and practical clinical problems as the disturbances of menstruation, tests for pregnancy, the climacteric, and cystic glandular hyperplasia of the endometrium. For the research worker the final chapter on methods of hormone assay will be particularly useful.

Of especial interest are the chapters which cover the history of the subject, menstruation, the physiology of the uterus, toxemias of pregnancy, and functional sterility.

Emphasis is placed throughout upon the interrelationships which exist between the endocrine glands; and experimental and clinical data are given due importance.

It is the reviewer's opinion that this book will be more useful as a reference than as a text. One also feels that the author writes much more convincingly and clearly of the clinical considerations than of the experimental and laboratory phases of his topic.

While typographical errors are present, and there is at times a somewhat confusing interchangeable use of terms designating groups of substances, the author, a well known clinical endocrinologist, has produced an interesting, useful, and readable book on this intricate subject.

J. E. S.

The Fundamentals of Internal Medicine. By WALLACE M. YATER, A.B., M.D., M.S. (in Medicine). 1021 pages; 25 × 17 cm. D. Appleton-Century Company, New York and London. 1938. Price, $9.00.

In his introduction to this new text, Dr. Yater says that it is designed primarily for the introduction of students to the subject of internal medicine, presenting the minimum amount of knowledge of clinical medicine a medical student or general practitioner should have at his fingertips. Most of the subject matter has been written by Dr. Yater himself, but eleven other authors have also contributed.

The reader is impressed by the book's brevity, clearness, orderliness and lack of confusing overdiscussion. Introduction to the different sections are written so that manifestations of diseases may be correlated with others in the same general groups. Symptomatology and differential diagnosis are stressed by means of diagnostic tables, outlines, and grouping of symptoms that are common to certain classes of disease. Presentations, however, are not from symptomatic, but from etiological and anatomic viewpoints.

The author has followed the English custom of including a chapter on diseases of the skin. There is also a short section on diseases of the ear by F. C. Schreiber,

and one on diseases of the eye, by J. A. Grear. These three unusual chapters are intended to correlate knowledge of these specialties with the subject of internal medicine.

Illustrations are used freely, and are uniformly excellent. The publishers should be congratulated on the roentgen-ray reproductions.

"Fundamentals of Internal Medicine" may be fully recommended to medical students. In the reviewer's opinion, it is a valuable addition to our teaching texts.

T. N. C.

The Chemistry of the Amino Acids and Proteins. Edited by CARL L. A. SCHMIDT, M.S., Ph.D. xxiv + 1031 pages; 17 × 26 cm. Charles C. Thomas, Springfield, Ill. 1938. Price, $7.50.

The present treatise represents a coöperative effort on the part of Dr. Carl L. A. Schmidt, editor and chief contributor, and sixteen individuals whose scientific interests lie chiefly in the field of the amino acids and the proteins. There are few people who are so well qualified by training and experience to write on this subject as are the editor and his collaborators. Their chief purpose was to bring together the scattered literature on the chemistry of the amino acids and proteins and to emphasize the more fundamental data by presentation in the same graphic or tabular form as in the original literature. The resultant compendium admirably covers the requirements of advanced students and research specialists interested in this particular field.

Most of the chapters are excellent. The first parts of the book present a discussion of the constitution, synthesis, isolation, analysis, reactions, biochemistry and physical characteristics of the amino acids and proteins. Then follow chapters on the amphoteric properties, electrochemistry, membrane equilibria, thermodynamics, dipolar structure and solubility of the same. Brief chapters on the relation of proteins to immunity and nutrition bring to a conclusion this most excellent book. Throughout it is much of the original work of the editor and his colleagues. It is the most substantial and modern book on the subject and is replete with references to the original literature. The entire volume has an air of competence and authority which could come only from writers with personal experience in these fields.

While the chemistry of the amino acids and proteins is so complete it almost defies criticism, the book contains but few and brief references to the physiology and metabolism of these substances. It is primarily written from the point of view of the physical chemist. Hence the present volume will be of less interest and value to the clinical chemist or the physician. The print of the book is easy to read and well set and the reproductions of the numerous figures are most excellent. A satisfactory author and subject index is also included.

E. G. S.

Diseases of the Blood and Atlas of Hematology. By ROY R. KRACKE, M.D., and HORTENSE ELTON GARVER, M.S. 532 pages; 26.5 × 18 cm. J. B. Lippincott Company, Philadelphia. 1937. Price, $15.00.

The authors have had the ambition to combine in one volume an atlas of hematology, a description of the cells of the blood in health and disease, a clinical description of the diseases of the blood and a manual of hematological technic. They have achieved this purpose within the compass of a volume of slightly over 500 pages. As an atlas the book is not an outstanding success. There are 44 colored plates which are reproductions of colored drawings from actual preparations. They are all of real value. The total number of cells shown, however, is not sufficient for an atlas and does not illustrate the many variations which are observed. In certain instances the reproductions are more diagrammatic than exact.

There is a well arranged and clearly written account of hematologic terminology, of the origin and development of blood cells and of their morphology. The description of the cells is quite concise and follows conventional lines.

The clinical descriptions of the blood diseases are all interesting and easily read. At times, as in the description of pernicious anemia, they seem somewhat abbreviated for the importance of the subject. The leukopenic diseases have always interested the senior author and it is only natural that this section should be fuller and more informative than others. The hypochromic anemias are likewise interestingly described. An unusual feature is the inclusion of a chapter on malaria.

The section on technic is a valuable one. The authors prefer slides to cover slips. A few line drawings in this section would have added to the clarity of some of the procedures.

All in all this is a volume which will hold its own in competition with the numerous recent books on hematology which have appeared in this country. It is an adequate monograph for the internist.

M. C. P.

Marihuana: America's New Drug Problem—A Sociologic Question with Its Basic Explanation Dependent on Biologic and Medical Principles. By ROBERT P. WALTON, Professor of Pharmacology, School of Medicine, University of Mississippi. 223 pages; 23.5 × 15.75 cm. J. B. Lippincott Company, Philadelphia. 1938. Price, $3.00.

The author has collected the available data on the addiction to the narcotic principle contained in the leaves and flowering tops of the hemp plant. At present there is a wave of addiction to smoking of marihuana cigarettes in various parts of the United States, so that the topic is a timely one. The history of this addiction, the many names given to it, what is known of its present world prevalence are topics dealt with in an interesting way. Popular, literary and scientific accounts of the drug's effects are given at some length. Its relation to crimes of violence seems well established. Its aphrodisiac effects are apparently the exception rather than the rule. There is a botanical description of the American hemp plant, *Cannabis sativa L.*, and pharmaceutical details connected with the preparations derived from the resin secreted by pluricellular hairs on the flowering tops. The subject of the therapeutic use of Cannabis is briefly dealt with.

The book is a valuable reference text for a subject of increasing social importance.

M. C. P

COLLEGE NEWS NOTES

Gifts to the College Library

Grateful acknowledgment is made of the receipt of the following gifts to the College Library of publications by members:

Books

Dr. Robert F. Loeb, F.A.C.P., New York City—"Martini's Principles and Practice of Physical Diagnosis";
Dr. Willard F. Machle (Associate), Cincinnati—"Industrial Hygiene: A Handbook of Hygiene and Toxicology for Engineers and Plant Managers";
Dr. David Riesman, F.A.C.P., Philadelphia—"Medicine in Modern Society";
Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor—"Diseases of the Blood."

Reprints

Dr. Walter L. Bierring, F.A.C.P., Des Moines, Iowa—1 reprint;
Dr. Louis F. Bishop, Jr., F.A.C.P., New York City—2 reprints (in duplicate);
Dr. Lucien Y. Dyrenforth (Associate), Jacksonville, Fla.—1 reprint;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;
Dr. George M. Lewis, F.A.C.P., New York City—3 reprints;
Dr. Bernard E. McGovern (Associate), San Fernando, Calif.—12 reprints;
Dr. Hyman A. Slesinger (Associate), Windber, Pa.—4 reprints;
Dr. Clyde A. Undine (Associate), Minneapolis, Minn.—1 reprint.

Among the most interesting additions to the College archives is a gift by Dr. Clement R. Jones, F.A.C.P., Pittsburgh, who has sent a bound volume of the "Transactions of the American Congress on Internal Medicine, 1916," being a detailed report of the annual congress of the College and the Congress, held in New York City, December 28–29, 1916. The volume also contains a copy of the Constitution and By-Laws of the Congress and a full list of the members of the Congress at that date. The American Congress on Internal Medicine was the affiliated organization through which the annual sessions of the American College of Physicians were organized and presented.

Dr. Jones also donated to the College archives Nos. 2 and 3 (July and November, 1920), Volume I, of the "Annals of Medicine," the first journal sponsored by the American College of Physicians. These journals each contain the full roster of members of the American College of Physicians and the American Congress on Internal Medicine. Besides containing a number of original articles, the journals carried a large number of abstracts of current literature.

Acknowledgment is also made of the receipt of a small book, "Palestine Today" by Elihu Grant, Stamford, Conn.

A very deeply appreciated gift to the College office was that of the Eighteenth Edition of Dorland's Illustrated Medical Dictionary, by the Publishers, W. B. Saunders Co., through Mr. J. A. Lutz, Sales Manager.

Sectional Meeting, Kansas Members

Under the Governorship of Dr. Thomas T. Holt, F.A.C.P., and with Dr. William C. Menninger, F.A.C.P., acting as host, Kansas Fellows and Associates held their annual sectional meeting at the Menninger Sanitarium, Topeka, Kan., November 4, with a good attendance and an excellent meeting. The program was as follows:

Starting at 10:00 a.m.

"Some Facts Concerning Gastric Acidity"—Dr. Philip W. Morgan, F.A.C.P., Emporia.

"Case Presentations:

1. Isolated Congenital Dextrocardia.
2. Ruptured Heart with Hemopericardium Following Coronary Occlusion"—Dr. Kenneth L. Druet (Associate), Salina.

"Headaches"—Dr. Norman Reider, Topeka.

Afternoon

"The Rôle of the Pituitary Gland in Clinical Medicine"—Dr. A. J. Revell (Associate), Pittsburgh.

"The Misuse of Digitalis"—Dr. Frank A. Trump, F.A.C.P., Ottawa.

"Gall Bladder Dysfunction"—Dr. Fred E. Angle, F.A.C.P., Kansas City.

"Case of Acute Idiopathic Hematoporphyria with Acute Ascending Paralysis"—Dr. Harold W. Palmer, F.A.C.P., Wichita.

"Cardiac Neuroses"—Dr. William C. Menninger, F.A.C.P., Topeka.

Luncheon was served at the Menninger Sanitarium; there was a social hour from five to six in the evening at the home of Dr. Menninger and dinner followed at the Jayhawk Hotel.

These sectional meetings are characterized by being partly scientific and partly social.

Sectional Meeting, Kentucky Members

Under the Governorship of Dr. C. W. Dowden, F.A.C.P., Fellows and Associates of the American College of Physicians from Kentucky held their annual meeting at Lexington, December 19, 1938. Thirty-five members were in attendance and the meeting was reported to be one of the finest in the six years that annual sectional meetings have been held in Kentucky. Kentucky was first, or certainly among the first, to hold these state meetings.

The program was as follows:

Starting at 3:00 p.m.

"Study of Glucose Tolerance Tests, Presentation of a Case of Diabetes Mellitus with Unusual Response to Insulin and Diet"—Dr. John W. Scott, F.A.C.P., and Dr. John Harvey, F.A.C.P.

"Tuberculous and Non-Tuberculous Tracheo-Bronchitis with Mediastinal Glands: Presentation of Two Cases"—Dr. Edward James Murray, F.A.C.P.

"Non-Tropical Sprue: Presentation of Two Cases"—Dr. Carl Hale Fortune, F.A.C.P.

Special Address on Angina Pectoris—Dr. William J. Kerr, F.A.C.P., President of the College.

A dinner followed in the evening at the LaFayette Hotel, given especially in honor of President Kerr. Dr. Carl Hale Fortune, F.A.C.P., was in charge of arrangements.

Dr. LeRoy S. Peters, F.A.C.P., Governor of the College for New Mexico, Albuquerque, is the retiring president of the Southwestern Medical Association, embracing the States of Arizona, New Mexico, West Texas and Northern Mexico.

Dr. Howell Randolph, F.A.C.P., Phoenix, Ariz., is the incoming president of the above organization, and Dr. Orville E. Egbert, F.A.C.P., El Paso, Tex., is the president-elect.

Dr. Carl J. Wiggers, F.A.C.P., Cleveland, was honored by his associates at a surprise tea on the afternoon of November 23, 1938, to celebrate the twentieth anniversary of his appointment as Professor of Physiology at Western Reserve University School of Medicine. On this occasion, Dr. Wiggers was presented with a book of photographs and letters of appreciation from the President of the University, the Dean of the School of Medicine, members and former members of the staff of the Department of Physiology and students who had done special work under his tutelage.

Dr. Wiggers has recently returned from a lecture trip to South America, where he visited Callao, Peru; Arica; Valparaiso; and Santiago, Chile. His itinerary took him by plane over the Andes to Buenos Aires. Dr. Wiggers delivered a series of lectures in Spanish on the applications of physiology to medicine in Buenos Aires, Santa Rosa, Rosario and Coroba. Chief among these were addresses before the VIth National Congress of Medicine.

Dr. August A. Werner, F.A.C.P., St. Louis, had an exhibit entitled "Theelin—Clinical Studies" before the scientific sections of the American Dental Association at St. Louis, Mo., October 24–28; the Interstate Post Graduate Medical Assembly at Philadelphia, October 31–November 4; and the Southern Medical Association at Oklahoma City, November 15–18.

During November Dr. George Herrmann, F.A.C.P., Galveston, Tex., delivered addresses before the Clinical and Pathological Society of the University of Southern California, the California Heart Association (of which Dr. B. O. Raulston, F.A.C.P., is President) and the Los Angeles County Medical Association. His titles before the above-mentioned societies were, respectively: "The Chemical Nature of Heart Failure"; "Treatment of the Failing Heart"; "Criteria for the Diagnosis of Coronary Thrombosis and Some Suggestions on Its Treatment."

Dr. Francis R. Dieuaide, F.A.C.P., is on leave from his post as professor of medicine and head of the department of medicine of the Peiping Union Medical College, Peiping, China, and spending the year as research associate in biological chemistry at Harvard University Medical School.

Col. Charles F. Craig (MC), U. S. A., Retired, F.A.C.P., has been retired as Emeritus Professor of Tropical Medicine at Tulane University of Louisiana School of Medicine and is now occupying his new home at 239 W. Lullwood Ave., San Antonio, Tex.

Dr. Z. Bercovitz, F.A.C.P., New York City, addressed the American Society of Tropical Medicine at Oklahoma City, November 15, on "The Differential Diagnosis of Amebic Dysentery from the Microscopic Examination of Bowel Discharges"; the Peoria Medical Society, at Peoria, Ill., November 21, on "The Diagnosis and Treatment of Chronic Ulcerative Colitis"; and the St. Louis Medical Society at St. Louis, November 22, on "The Diagnosis and Treatment of Chronic Ulcerative Colitis."

Dr. Anthony Bassler, F.A.C.P., President of the National Gastro-enterological Association, and Dr. Samuel Weiss, F.A.C.P., Editor of the *Review of Gastroenterology*, both of New York City, have been honored by the Italian Gastroenterological Society (Italy), by being elected Honorary Fellows.

Dr. Samuel M. Feinberg, F.A.C.P., Chicago, was the guest speaker at the discussion and meeting of the Oklahoma Allergists, November 17, 1938, held in connection with the Southern Medical Association. His subject was "Clinical Aspects of Mould Allergy."

Dr. Henry M. Moses, F.A.C.P., has been reëlected Director of Medical Service at Kings County Hospital (Brooklyn). He is also Consultant in Medicine at the Wyckoff Heights Hospital (Brooklyn).

Dr. A. J. Logie (Associate), Director, Division of Tuberculosis, Florida State Board of Health, participated in the scientific program of the Thomas County Medical Society, Thomasville, Ga., December 21, 1938, speaking upon "The Changing Picture of Tuberculosis."

Dr. H. I. Spector (Associate), St. Louis, was elected President of the Mississippi Valley Conference on Tuberculosis at its recent annual meeting held in St. Louis.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., has been elected President of the Northern Medical Association of Philadelphia for 1939. The Association will begin its 93rd year, having been founded in 1846. It is one of the oldest medical societies in Pennsylvania.

Dr. Frank S. Horvath, F.A.C.P., Washington, D. C., presented the following papers before the alumni of Georgetown University Medical School during the past autumn: "Unusual Electrocardiograms" and "Arterial Hypotension." Dr. Horvath addressed the George Washington Medical Society on November 19 on "Criteria for the Diagnosis of Mitral and Aortic Valvular Disease." The murmurs were demonstrated by the electric stethoscope and amplified.

The Fourth Annual Postgraduate Institute of The Philadelphia County Medical Society will be held March 13–17, inclusive, 1939. The subjects to be considered are those embraced by the terms "Blood Dyscrasias" and "Metabolic Disorders." These will be further subdivided for convenience in instruction into eighty-six clinical lectures, with open forum discussion for each topic, delivered by as many individual specialists of national distinction.

Dr. Rufus S. Reeves, F.A.C.P., is the Director of the Postgraduate Institute and President-Elect of the Society.

Dr. Ralph Pemberton, F.A.C.P., Philadelphia, addressed the Pittsburgh Academy of Medicine, December 13, 1938, on "The Syndrome of Arthritis."

Duke Hospital, at Durham, N. C., has just announced plans for a new 200-room addition to the present hospital building, providing from 100 to 120 new beds and raising the total capacity of the hospital to more than 550 beds. The new addition will provide for the expansion of the Hospital's clinic services. During the past two years there has been an almost constant waiting list of patients at Duke Hospital from every county in the State as well as from outside states. The addition will utilize the latest developments in mechanical and electrical equipment and in its arrangement.

A number of Fellows of the American College of Physicians are active on the Faculty of the Medical School and on the Staff of the Hospital. At the main entrance to the Duke Hospital the seals of the American College of Physicians and of the American College of Surgeons are sculptured in the stonework on either side.

Louis F. Bishop, Jr., M.D., spoke on "The Management of Coronary Artery Disease" before the Waterbury Medical Association at Waterbury, Connecticut, on Thursday, December 8. Dr. Bishop also spoke at the Goshen Hospital on December 6, on "Electrocardiograms in Heart Disease."

New Elections to College Membership

At a meeting of the Board of Regents December 18, 1938, at the headquarters building, Philadelphia, the following candidates were regularly elected to the class indicated:

Elections to Fellowship

December 18, 1938

Candidates	*Sponsors*
Alabama	
Marion Tabb Davidson, Birmingham	Seale Harris, James S. McLester, Groesbeck Walsh, Fred Wilkerson
Edgar Gilmore Givhan, Jr., Birmingham	James S. McLester, Joseph E. Hirsh, Fred Wilkerson
James Bowron McLester, Birmingham	James E. Paullin, Joseph E. Hirsh, Fred Wilkerson
Arizona	
Jesse Dewey Hamer, Phoenix	W. Warner Watkins, Harlan P. Mills, Fred G. Holmes
California	
Joe Edmund Walker, Long Beach	Noel F. Shambaugh, Fred B. Clarke, James F. Churchill
Leland Potts Hawkins, Los Angeles	Carl R. Howson, Raymond G. Taylor, James F. Churchill
Mast Wolfson, Monterey	Arthur L. Bloomfield, Thomas Addis, Ernest H. Falconer
Arthur Marlow, San Diego	Claude E. Forkner, George R. Minot, James F. Churchill
Raymond Arthur Sands, Santa Monica	Roland Cummings, Samuel M. Alter, James F. Churchill
Colorado	
Paul A. Draper, Colorado Springs	A. Lee Briskman, Gerald B. Webb, James J. Waring
William Corr Service, Colorado Springs	G. Burton Gilbert, John A. Sevier, James J. Waring
John Palmer Hilton, Denver	Wilfred S. Dennis, Glaister H. Ashley, James J. Waring
Connecticut	
Walter Ralph Steiner, Hartford	George Blumer, John A. Wentworth, Francis G. Blake
District of Columbia	
John Richard Cavanagh, Washington	William M. Ballinger, Lester Neuman, Wallace M. Yater
Leslie Howson French, Washington	Oscar B. Hunter, J. B. Glenn, Wallace M. Yater
Ernest Elvin Hadley, Washington	Joseph L. Gilbert, A. C. Christie, Wallace M. Yater
Frank Stephen Horvath, Washington	James Alexander Lyon, Tomás Cajigas, Wallace M. Yater

Candidates	*Sponsors*
Earl Richard Templeton, Washington	Wm. M. Ballinger, M. W. Perry, Wallace M. Yater
George Louis Weller, Jr., Washington	W. A. Bloedorn, Walter Freeman, Wallace M. Yater
Medical Corps, U. S. Army	
Joseph Hall Whiteley, Corozal, C. Z.	C. R. Reynolds
U. S. Public Health Service	
John William Trask, Chelsea, Mass.	Thomas Parran
Georgia	
Launcelot Minor Blackford, Atlanta	Russell H. Oppenheimer, Trimble Johnson, Glenville Giddings
Thomas Sterling Claiborne, Atlanta	Roy S. Leadingham, John B. Fitts, James E. Paullin, Glenville Giddings
William Johnston Cranston, Augusta	V. P. Sydenstricker, Eugene E. Murphey, Glenville Giddings
Hartwell Joiner, Gainesville	H. C. Sauls, John B. Fitts, Glenville Giddings
Warren Monroe Gilbert, Rome	John B. Fitts, H. C. Sauls, Glenville Giddings
Illinois	
Vernon Lawrence Evans, Aurora	S. L. Gabby, J. Donald Milligan, James G. Carr
Fred Eugene Ball, Jr., Chicago	Joseph A. Capps, Arthur R. Elliott, James G. Carr
Roy R. Jamieson, Chicago	David E. Markson, Nathan S. Davis, III, James G. Carr
Henry Lenzen Schmitz, Chicago	Robert S. Berghoff, Fred M. Drennan, James G. Carr
James Bernard Berardi, Dwight	W. E. Kendall, Edward W. Hollingsworth, James G. Carr
Harry Anthony Durkin, Peoria	Henry H. Thomas, Jr., Paul Dudley White, Samuel E. Munson
Emmet Forrest Pearson, Springfield	Alfred Goldman, H. L. Alexander, David P. Barr, Samuel E. Munson
Kansas	
William Hackney Algie, Kansas City	P. T. Bohan, Fred J. McEwen, Thomas T. Holt
Fred Ernest Angle, Kansas City	P. T. Bohan, Harold W. Palmer, Thomas T. Holt
Kentucky	
Max L. Garon, Louisville	Morris Flexner, J. Murray Kinsman, C. W. Dowden
Frederick George Speidel, Louisville	Oscar O. Miller, Arthur Clayton McCarty, C. W. Dowden
Maryland	
Raymond Hussey, Baltimore	Wm. S. Love, Jr., Thomas P. Sprunt, Henry M. Thomas, Jr.
Massachusetts	
Egon Emil Kattwinkel, Auburndale	Dwight O'Hara, William D. Reid, William B. Breed

Candidates	*Sponsors*
Maxwell Finland, Boston	George R. Minot, Soma Weiss, William B. Breed
Jerome Andrew Whitney, Longmeadow	Laurence D. Chapin, George L. Steele, William B. Breed
Milton James Quinn, Winchester	Frederick T. Lord, Donald S. King, William B. Breed
	MICHIGAN
Bruce Hutchinson Douglas, Detroit	Wm. A. Evans, Lawrence Reynolds, Henry R. Carstens
David Jacob Sandweiss, Detroit	William H. Gordon, Laurence F. Segar, Henry R. Carstens
Robert Jacob Schneck, Detroit	Richard M. McKean, Douglas Donald, Henry R. Carstens
Joseph Francis Whinery, Grand Rapids	Joseph B. Whinery, Burton R. Corbus, Henry R. Carstens
	MINNESOTA
William Arnold Stafne, Moorhead	Russell M. Wilder, Bayard T. Horton, E. L. Tuohy
Edwin John Kepler, Rochester	E. V. Allen, Russell M. Wilder, E. L. Tuohy
Herman John Moersch, Rochester	E. V. Allen, F. W. Gaarde, E. L. Tuohy
Howard Miller Odel, Rochester	A. R. Barnes, E. V. Allen, E. L. Tuohy
Edwin J. Simons, Swanville	J. A. Myers, S. Marx White, E. L. Tuohy
	MISSOURI
Hyman I. Spector, St. Louis	Daniel L. Sexton, Alphonse McMahon, David Barr, A. C. Griffith
	NEBRASKA
Joseph Daniel McCarthy, Omaha	M. C. Howard, F. W. Niehaus, Warren Thompson
	NEW JERSEY
Harold Korb Eynon, Collingswood	G. O. Favorite, Carl C. Fischer, Clarence L. Andrews
Carlyle Morris, Metuchen	Frederick L. Brown, Karl Rothschild, Clarence L. Andrews
Frederic A. Alling, Newark	Manfred Kraemer, Edward C. Klein, Jr., Clarence L. Andrews
	NEW YORK
George Edward Anderson, Brooklyn	Frank Bethel Cross, Tasker Howard, C. F. Tenney
Harold Russell Merwarth, Brooklyn	Frank Bethel Cross, Tasker Howard, C. F. Tenney
Bernard Sternberg, Brooklyn	David Gingold, Morris M. Banowitch, C. F. Tenney
Earl Bradley Erskine, Jamaica	Claude E. Forkner, Goodwin A. Distler, C. F. Tenney
Louis Ashley Van Kleeck, Manhasset	Louis H. Bauer, Everett C. Jessup, C. F. Tenney
Burrill B. Crohn, New York	A. F. R. Andresen, T. Grier Miller, C. F. Tenney
John Staige Davis, Jr., New York	Lewis F. Frissell, Walter G. Lough, C. F. Tenney
John Leonard Kantor, New York	A. F. R. Andresen, M. D. Levy, C. F. Tenney
Thomas Hodge McGavack, New York	Linn J. Boyd, Milton J. Raisbeck, C. F. Tenney

Candidates	*Sponsors*
John McDowell McKinney, New York	Charles A. McKendree, Robert F. Loeb, C. F. Tenney
Henry Barber Richardson, New York	John A. Wentworth, Joseph H. Pratt, Eugene F. Du Bois, C. F. Tenney
Zachary Sagal, New York	Herman O. Mosenthal, Walter G. Lough, C. F. Tenney
Theresa Scanlan, New York	Thomas T. Mackie, Joseph Lintz, C. F. Tenney
Philipp J. R. Schmahl, New York	Linn J. Boyd, Milton J. Raisbeck, C. F. Tenney
Cornelius Horace Traeger, New York	R. Garfield Snyder, Howard F. Shattuck, C. F. Tenney
Harry Eduarde Ungerleider, New York	Arthur M. Master, George Baehr, C. F. Tenney
S. Bernard Wortis, New York	Charles A. McKendree, Robert F. Loeb, C. F. Tenney
North Carolina	
Edward Sandling King, Wake Forest	Verne S. Caviness, Thurman Kitchin, C. H. Cocke
Ohio	
Fay Atkinson LeFevre, Cleveland	Russell L. Haden, C. L. Hartsock, A. B. Brower
Ralph Martin Watkins, Cleveland	Chas. T. Way, H. D. Piercy, A. B. Brower
Oklahoma	
Samuel Charlton Shepard, Tulsa	Russell C. Pigford, E. Rankin Denny, Lea A. Riely
Oregon	
Ernest Lloyd Boylen, Portland	Ralph C. Matson, Homer P. Rush, T. Homer Coffen
Blair Holcomb, Portland	Homer P. Rush, John H. Fitzgibbon, T. Homer Coffen
Merl Lonner Margason, Portland	N. W. Jones, Laurence Selling, T. Homer Coffen
Merle Wayland Moore, Portland	Homer P. Rush, John H. Fitzgibbon, T. Homer Coffen
Pennsylvania	
Paul H. Parker, Jenkintown	H. B. Wilmer, John Eiman, Geo. Morris Piersol, Edward L. Bortz
John Olen Woods, New Castle	Wayne W. Bissell, Eliah Kaplan, R. R. Snowden
Kenneth Ellmaker Appel, Philadelphia	Edward A. Strecker, David A. Cooper, Edward L. Bortz
Walter Lawrence Cahall, Philadelphia	Thomas M. McMillan, H. B. Wilmer, Edward L. Bortz
Harold R. Keeler, Philadelphia	Thomas Fitz-Hugh, Jr., Edward Rose, Geo. Morris Piersol, Edward L. Bortz
Charles Fay Nichols, Philadelphia	Thomas Klein, Thomas M. McMillan, Edward L. Bortz
John Herbert Leyda Heintzelman, Pittsburgh	Frank A. Evans, James M. Strang, E. Bosworth McCready, R. R. Snowden

Candidates	*Sponsors*
RHODE ISLAND	
Russell Stanton Bray, Providence	Herman A. Lawson, Charles F. Gormly, Alex. M. Burgess
Henry L. C. Weyler, Providence	Charles F. Gormly, Harvey E. Wellman, Alex. M. Burgess
SOUTH CAROLINA	
Francis Eugene Zemp, Columbia	J. Heyward Gibbes, O. B. Mayer, Kenneth M. Lynch
TENNESSEE	
Charles Roberts Thomas, Chattanooga	Leopold Shumacker, Franklin B. Bogart, J. O. Manier
TEXAS	
William Bluford Adamson, Abilene	Erle D. Sellers, T. C. Terrell, Moise D. Levy
Wendell Heath Paige, Brownwood	Will S. Horn, T. C. Terrell, C. T. Stone, Moise D. Levy
James John Gorman, El Paso	O. E. Egbert, C. M. Hendricks, Moise D. Levy
Julian Cox Barton, San Antonio	Lee Rice, Joe Kopecky, Moise D. Levy
Edgar Marion McPeak, San Antonio	Lee Rice, Joe Kopecky, Moise D. Levy
VIRGINIA	
James Newton Williams, Richmond	R. Finley Gayle, Jr., Dean B. Cole, J. Morrison Hutcheson
WASHINGTON	
John Ernest Nelson, Seattle	Frederick Slyfield, Homer Wheelon, C. E. Watts
WEST VIRGINIA	
Dudley Curtis Ashton, Beckley	J. Morrison Hutcheson, Dean B. Cole, Walter E. Vest
George Fordham, Powellton	John W. Moore, A. A. Shawkey, Walter E. Vest
Charles Belson Chapman, Welch	Albert M. Snell, A. R. Barnes, Walter E. Vest
Howard Russell Sauder, Wheeling	D. A. MacGregor, W. M. Sheppe, Walter E. Vest
WISCONSIN	
Marcos Fernan-Nunez, Milwaukee	Francis D. Murphy, W. J. Egan, Rock Sleyster
John Carl Grill, Milwaukee	Joseph Lettenberger, Francis D. Murphy, Rock Sleyster
Theodore John Pfeffer, Racine	Elmer G. Senty, A. R. Barnes, Rock Sleyster
DOMINION OF CANADA	
Prince Edward Island	
John Wendell McKenzie, Charlottetown	A. B. Walter, R. J. Collins, H. A. Farris
QUEBEC	
Walter de Mouilpied Scriver, Montreal	Arthur T. Henderson, R. H. M. Hardisty, Charles F. Moffatt

Resolved, that the following list of 10 be and herewith are elected to Fellowship in the American College of Physicians as of March 26, 1939.

Candidates	*Sponsors*
	ILLINOIS
Harold Charles Lueth, Evanston	N. S. Davis, III, Laurence E. Hines, James G. Carr
	MICHIGAN
Walter Merritt Bartlett, Benton Harbor	Russell L. Cecil, A. C. Curtis, Henry R. Carstens
Clarence E. Reyner, Detroit	Frank R. Menagh, F. Janney Smith, Henry R. Carstens
	MINNESOTA
Alexander Edward Brown, Rochester	E. V. Allen, H. C. Habein, E. L. Tuohy
	NEW YORK
Herbert Robert Edwards, New York	J. K. Deegan, J. Burns Amberson, Jr., C. F. Tenney
Oswald Roberts Jones, New York	James R. Scott, J. Burns Amberson, Jr., C. F. Tenney
Charles Aden Poindexter, New York	James G. Carr, Irving S. Wright, C. F. Tenney
	OKLAHOMA
Elmer Ray Musick, Oklahoma City	Wann Langston, John E. Heatley, Lea A. Riely
	PENNSYLVANIA
Russell Sherwood Anderson, Erie	George A. Sherman, George F. Stoney, R. R. Snowden
	VERMONT
Ellsworth Lyman Amidon, Burlington	C. H. Beecher, H. R. Ryan, Paul K. French

ELECTIONS TO ASSOCIATESHIP

December 18, 1938

	ALABAMA
Hunt Cleveland, Anniston	Mark A. Brown, Leon Schiff, Fred Wilkerson
	ARIZONA
Orin Jocevious Farness, Tucson	Roland Davison, Charles W. Mills, Fred G. Holmes
William Roy Hewitt, Tucson	Virgil G. Presson, Samuel H. Watson, Fred G. Holmes
	ARKANSAS
Leon Earl King, Hot Springs National Park	Geo. B. Fletcher, Euclid M. Smith, Oliver C. Melson
	CALIFORNIA
Horace Bicknell Cates, Los Angeles	E. Richmond Ware, William H. Leake, James F. Churchill
Thomas B. Cunnane, Los Angeles	J. Mark Lacey, Robert W. Langley, James F. Churchill

Candidates	*Sponsors*
Emmett LeRoy Schield, Pomona	Charles R. Castlen, E. W. Hayes, James F. Churchill
E. Minton Fetter, San Diego	R. H. Sundberg, W. H. Barrow, James F. Churchill
Lyle Andrew Baker, San Francisco	William H. Leake, Chas. M. Griffith, Ernest H. Falconer
Buford Haven Wardrip, San Jose	Earl O. G. Schmitt, Harold G. Trimble, Ernest H. Falconer
	COLORADO
Roger Sherman Whitney, Colorado Springs	James H. Brown, A. Lee Briskman, James J. Waring
Robert William Gordon, Denver	Ward Darley, James J. Waring, Gerald B. Webb
Abe Ravin, Denver	James R. Arneill, R. W. Arndt, James J. Waring
John I. Zarit, Denver	Mathew A. Spangelberger, Harry Gauss, James J. Waring
	CONNECTICUT
Charles Tiffany Bingham, Hartford	John A. Wentworth, G. Gardiner Russell, Francis G. Blake
Samuel Donner, Hartford	O. G. Wiedman, Orin R. Witter, Francis G. Blake
Maxwell Overlock Phelps, Hartford	John A. Wentworth, Orin R. Witter, Francis G. Blake
Peter J. Steincrohn, Hartford	Orin R. Witter, O. G. Wiedman, Francis G. Blake
Robert H. Jordan, New Haven	Theodore S. Evans, C. J. Bartlett, Francis G. Blake
Charles Arthur Breck, Wallingford	J. Alfred Wilson, Cole B. Gibson, Francis G. Blake
	DISTRICT OF COLUMBIA
Theodore Judson Abernethy, Washington	Walter K. Myers, Henry M. Thomas, Jr., Wallace M. Yater
Worth Bagley Daniels, Washington	W. A. Bloedorn, A. C. Christie, Wallace M. Yater
Clayton Bernard Ethridge, Washington	J. Winthrop Peabody, W. A. Bloedorn, Wallace M. Yater
Henry Anatol Monat, Washington	George W. Calver, C. B. Conklin, Wallace M. Yater
	FLORIDA
Karl Boyles Hanson, Jacksonville	Louie Limbaugh, Clayton E. Royce, T. Z. Cason
Franz Hahr, Stewart, Miami	P. B. Welch, Kenneth Phillips, T. Z. Cason
Paul K. Jenkins, Miami Beach	C. F. Roche, P. B. Welch, T. Z. Cason
Harold A. Ryan, Miami Beach	C. F. Roche, P. B. Welch, T. Z. Cason
Albert W. Wallace, Miami Beach	C. F. Roche, P. B. Welch, T. Z. Cason
	GEORGIA
Arthur Park McGinty, Atlanta	Russell H. Oppenheimer, John B. Fitts, Glenville Giddings
Bernard Preston Wolff, Atlanta	Roy S. Leadingham, H. C. Sauls, Glenville Giddings
Hervey Milton Cleckley, Augusta	Edgar R. Pund, J. D. Gray, Glenville Giddings
Harry Taylor Harper, Jr., Augusta	V. P. Sydenstricker, J. D. Gray, Edgar R. Pund, Glenville Giddings

Candidates	*Sponsors*
Paul Sadler Kemp, Macon	James A. Fountain, J. D. Gray, Glenville Giddings
James Miller Byne, Jr., Waynesboro	Guy G. Lunsford, Edgar R. Pund, Glenville Giddings
	ILLINOIS
J. Bailey Carter, Chicago	A. J. Carlson, W. O. Thompson, James G. Carr
Frank B. Queen, Chicago	W. Bernard Yegge, James R. Arneill, James J. Waring
Theodore Robert Van Dellen, Chicago	J. Roscoe Miller, Laurence E. Hines, James G. Carr
Willard L. Wood, Chicago	W. O. Thompson, L. C. Gatewood, James G. Carr
Clarence Elliott Bell, Decatur	Otis O. Stanley, Cecil M. Jack, Samuel E. Munson
Paul Spottswood Rhoads, Evanston	Lowell D. Snorf, Arthur E. Mahle, James G. Carr
John Edward McCorvie, Peoria	George Parker, Orville Barbour, Samuel E. Munson
	KANSAS
John McGill Porter, Concordia	William C. Menninger, Fred J. McEwen, Thomas T. Holt
Aaron Alfred Sprong, Sterling	Henry N. Tihen, Harold W. Palmer, Thomas T. Holt
Earl L. Mills, Wichita	Ferdinand C. Helwig, Henry N. Tihen, Thomas T. Holt
	KENTUCKY
William Austin Bloch, Louisville	Jno. J. Moren, Morris Flexner, C. W. Dowden
Adolph B. Loveman, Louisville	J. Murray Kinsman, Morris Flexner, C. W. Dowden
David S. Traub, Louisville	J. Murray Kinsman, W. E. Gardner, C. W. Dowden
	LOUISIANA
Oscar Blitz, New Orleans	B. R. Heninger, Edgar Hull, J. E. Knighton
Donovan Clarence Browne, New Orleans	Randolph Lyons, J. H. Musser, J. E. Knighton
William Howard Gillentine, New Orleans	J. H. Musser, Philip H. Jones, J. E. Knighton
Isidore Leon Robbins, New Orleans	J. H. Musser, Philip H. Jones, J. E. Knighton
Herbert John Schattenberg, New Orleans	Charles W. Duval, J. H. Musser, J. E. Knighton
	MARYLAND
Marshall Paul Byerly, Baltimore	William S. Love, Jr., William H. Smith, Henry M. Thomas, Jr.
Henry Mathies Hensen, Baltimore	Wetherbee Fort, Walter A. Baetjer, Henry M. Thomas, Jr.
Robert Bruce Mitchell, Jr., Baltimore	William S. Love, Jr., T. Nelson Carey, Henry M. Thomas, Jr.
Wendell Stanley Muncie, Baltimore	George W. Thorn, Thomas P. Sprunt, Henry M. Thomas, Jr.
Hugh Grigsby Whitehead, Jr., Baltimore	Richard France, Chas. W. Wainwright, Henry M. Thomas, Jr.

Candidates	*Sponsors*
Charles H. Conley, Jr., Buckeystown	R. W. Baer, Sydney R. Miller, Henry M. Thomas, Jr.
John Harlan Hornbaker, Hagerstown	R. S. Stauffer, Victor F. Cullen, Henry M. Thomas, Jr.
Lawrence Foss Woolley, Towson	Ross McC. Chapman, John T. King, Henry M. Thomas, Jr.
	MASSACHUSETTS
Allen Gilbert Brailey, Boston	Donald S. King, Wyman Richardson, William B. Breed
John W. Cass, Jr., Boston	Dwight L. Siscoe, J. H. Means, William B. Breed
Harold Joseph Jeghers, Boston	Chester S. Keefer, John A. Foley, William B. Breed
William Timothy O'Halloran, Boston	John A. Foley, Chester S. Keefer, William B. Breed
Richard Pratt Stetson, Boston	George R. Minot, Soma Weiss, William B. Breed
Lowrey Frederick Davenport, Brookline	Donald S. King, Henry A. Christian, William B. Breed
	MICHIGAN
Robert S. Ballmer, Ann Arbor	Arthur C. Curtis, Herman H. Riecker, Henry R. Carstens
Abraham Becker, Ann Arbor	Arthur C. Curtis, Raphael Isaacs, Henry R. Carstens
Edward Mahon Kline, Ann Arbor	Frank N. Wilson, Cyrus C. Sturgis, Henry R. Carstens
Christopher Parnall, Jr., Ann Arbor	Arthur C. Curtis, Cyrus C. Sturgis, Henry R. Carstens
Spencer Harley Wagar, Ann Arbor	Frank N. Wilson, Cyrus C. Sturgis, Henry R. Carstens
George Willard Slagle, Battle Creek	John V. Fopeano, M. A. Mortensen, Henry R. Carstens
Sidney Adler, Detroit	Hugo A. Freund, Robert C. Moehlig, Henry R. Carstens
James Ian Baltz, Detroit	Frank J. Sladen, John G. Mateer, Henry R. Carstens
C. Herbert Belknap, Detroit	George Barrie Hoops, Rollin H. Stevens, Henry R. Carstens
Benjamin I. Johnstone, Detroit	F. Janney Smith, Warren Cooksey, Henry R. Carstens
Curt Paul Schneider, Detroit	George Barrie Hoops, Rollin H. Stevens, Henry R. Carstens
Emil M. Shebesta, Detroit	Rollin H. Stevens, George Barrie Hoops, Henry R. Carstens
Lloyd Bennett Young, Detroit	George Barrie Hoops, Rollin H. Stevens, Henry R. Carstens
Benjamin Elmer Goodrich, Pleasant Ridge	F. Janney Smith, Frank R. Menagh, Henry R. Carstens
Francis James Fitzpatrick, Pontiac	Harold R. Roehm, George A. Sherman, Henry R. Carstens
Evert Waitman Meredith, Port Huron	Frank J. Sladen, F. Janney Smith, Henry R. Carstens

Candidates	*Sponsors*
	MINNESOTA
Clarence Wilber Erickson, Rochester	E. V. Allen, George B. Eusterman, E. L. Tuohy
Horton Corwin Hinshaw, Rochester	E. V. Allen, A. R. Barnes, E. L. Tuohy
Thomas Douglas Kendrick, Rochester	R. M. Wilder, E. V. Allen, E. L. Tuohy
Alexander Robinson MacLean, Rochester	E. V. Allen, Henry W. Woltman, E. L. Tuohy
Arthur Seldon Mann, Rochester	Samuel F. Haines, E. V. Allen, E. L. Tuohy
Arthur Martin Olsen, Rochester	E. V. Allen, F. A. Willius, E. L. Tuohy
Edward Frank Rosenberg, Rochester	R. M. Wilder, E. V. Allen, E. L. Tuohy
Louis Dysart Vaughn, Rochester	E. V. Allen, D. M. Berkman, E. L. Tuohy
John Joseph Walsh, Rochester	Frank J. Heck, Philip S. Hench, E. L. Tuohy
Richard Nathaniel Washburn, Rochester	Samuel F. Haines, Charles H. Watkins, E. L. Tuohy
Donald J. Wolfram, Rochester	A. R. Barnes, Austin C. Davis, E. L. Tuohy
	MISSISSIPPI
Wesley Wayne Lake, Pass Christian	Ben R. Heninger, Randolph Lyons, G. W. F. Rembert
	MISSOURI
William Byrne Brown, Columbia	Elsworth S. Smith, Dan G. Stine, David Barr, A. C. Griffith
Michael Bernreiter, Kansas City	Sam H. Snider, Wilson A. Myers, A. C. Griffith
Leon Bromberg, St. Louis	Walter M. Simpson, Harry L. Alexander, A. C. Griffith
Francis B. Camp, Springfield	G. B. Lemmon, A. L. Anderson, A. C. Griffith
	MONTANA
Charles Francis Little, Great Falls	H. W. Gregg, A. R. Foss, Louis H. Fligman
Meredith Benjamin Hesdorffer, Missoula	W. Hiemstra, A. R. Foss, Louis H. Fligman
	NEBRASKA
Willis D. Wright, Omaha	Frederick W. Niehaus, Warren Thompson, Adolph Sachs
	NEW HAMPSHIRE
Harold David Levine, Bristol	Henry A. Christian, Fred E. Clow, Robert B. Kerr
Joseph Dunbar Shields, Jr., Concord	Fred E. Clow, H. W. N. Bennett, Robert B. Kerr
	NEW JERSEY
Samuel Cohen, Jersey City	Thomas J. White, J. Burns Amberson, Clarence L. Andrews
Arthur Milton Kraut, Jersey City	Eugene J. Luippold, Harry J. Perlberg, Clarence L. Andrews
Charles A. Landshof, Jersey City	Thomas J. White, Henry T. Von Deesten, Clarence L. Andrews
Theodore Richard Failmezger, Madison	George H. Lathrope, Irving S. Wright, Clarence L. Andrews
Ralph Irving Alford, Montclair	Lewis W. Brown, Edward C. Klein, Jr., Clarence L. Andrews
Elizabeth Brakeley, Montclair	Harvey M. Ewing, Josephine B. Neal, Clarence L. Andrews

Candidates	*Sponsors*
	NEW MEXICO
Walter I. Werner, Albuquerque	J. R. Van Atta, Carl Mulky, L. S. Peters
	NEW YORK
Samuel Perkins Bailey, Brooklyn	M. M. Banowitch, Henry Joachim, C. F. Tenney
Benjamin M. Bernstein, Brooklyn	Harry R. Litchfield, Anthony Bassler, C. F. Tenney
Benjamin M. Eis, Brooklyn	Simon R. Blatteis, Henry Joachim, C. F. Tenney
Elliston Farrell, Brooklyn	Tasker Howard, J. Hamilton Crawford, C. F. Tenney
Saverio Charles Franco, Brooklyn	A. F. R. Andresen, Frederick Schroeder, C. F. Tenney
Irving Greenfield, Brooklyn	Tasker Howard, Irving Gray, C. F. Tenney
Alfred P. Ingegno, Brooklyn	John B. D'Albora, Tasker Howard, C. F. Tenney
Leo Loewe, Brooklyn	Simon R. Blatteis, Henry Joachim, C. F. Tenney
Emanuel Schwartz, Brooklyn	A. F. R. Andresen, Tasker Howard, C. F. Tenney
Edmund Lester Shlevin, Brooklyn	Simon R. Blatteis, Henry Joachim, C. F. Tenney
Lawrence Edgar Hummel, Buffalo	A. H. Aaron, Clayton W. Greene, Nelson G. Russell
Richard Harry Schmit, Buffalo	Roy G. Pfotzer, John M. Mesmer, Nelson G. Russell
Charles Wesley Martin, Far Rockaway	Louis H. Bauer, Everett C. Jessup, C. F. Tenney
Warren Irving Titus, Glen Cove, L. I.	Frank Bethel Cross, Everett C. Jessup, C. F. Tenney
James Burnett Shields, Glens Falls	Morris Maslon, G. A. Chapman, C. F. Tenney
David Fertig, Hartsdale	Irving S. Wright, F. M. Jordan, C. F. Tenney
Dwight Turney Bonham, Hempstead	Willard J. Davies, Roy D. Grimmer, C. F. Tenney
Benjamin R. Allison, Hewlett, L. I.	Henry T. Chickering, Everett C. Jessup, C. F. Tenney
John Leonard Byrnes, Hudson Falls	Morris Maslon, W. H. Ordway, C. F. Tenney
Jacob Ernest Nadler, Jackson Heights	Arthur C. DeGraff, Clarence E. de la Chapelle, C. F. Tenney
John William Pendleton Love, Johnson City	Ronald L. Hamilton, C. H. Berlinghof, C. F. Tenney
Harold Albert Butman, Manhasset	Louis H. Bauer, Willard J. Davies, C. F. Tenney
Edgar Willis Hainlen, Mount Morris	J. K. Deegan, J. Burns Amberson, Jr., Nelson G. Russell
Harold Brandaleone, New York	Elaine P. Ralli, Clarence E. de la Chapelle, C. F. Tenney
Maurice Bruger, New York	Walter G. Lough, Milton A. Bridges, C. F. Tenney
John De Paul Currence, New York	Walter G. Lough, Irving S. Wright, C. F. Tenney
Morris Lionel Drazin, New York	Carl Boettiger, Charles M. Levine, C. F. Tenney
Mack Lipkin, New York	Walter G. Lough, Carl H. Greene, C. F. Tenney
Leon Arthur Salmon, New York	Charles A. McKendree, A. Wilbur Duryee, C. F. Tenney
William Andrew Somerville, New York	M. Coleman Harris, Josephine B. Neal, C. F. Tenney
William von Stein, New York	Arthur F. Chace, Irving S. Wright, C. F. Tenney
Edwin Wilder Gates, Niagara Falls	Clayton W. Greene, W. R. Scott, Nelson G. Russell

Candidates	*Sponsors*
Eugene Calvelli, Port Washington	Arthur C. DeGraff, Currier McEwen, C. F. Tenney
Lyndon Harwood Thatcher, Poughkeepsie	Scott L. Smith, C. Knight Deyo, C. F. Tenney
Doran J. Stephens, Rochester	Wm. S. McCann, Charles B. F. Gibbs, Nelson G. Russell
Daniel Milton Brumfiel, Saranac Lake	Wm. S. McCann, F. Janney Smith, Nelson G. Russell
North Carolina	
Allyn Blythe Choate, Charlotte	Edward J. Wannamaker, T. Preston White, A. A. Barron, C. H. Cocke
Frank Baker Marsh, Salisbury	I. H. Manning, D. Waldo Holt, C. H. Cocke
Charles Darwin Thomas, Sanatorium	P. P. McCain, W. T. Rainey, C. H. Cocke
North Dakota	
Paul Jean Breslich, Minot	Paul H. Rowe, Robert B. Radl, Julius O. Arnson
Ohio	
Karl Duren Way, Akron	F. C. Potter, Joseph M. Ulrich, A. B. Brower
William Parrish Garver, Cleveland	R. W. Kissane, John A. Toomey, A. B. Brower
Mortimer L. Siegel, Cleveland	Harold Feil, Chas. T. Way, A. B. Brower
Carl Vernon Moore, Jr., Columbus	Charles A. Doan, B. K. Wiseman, A. B. Brower
Harold Fredrick Koppe, Dayton	Walter M. Simpson, Benedict Olch, A. B. Brower
Nelson David Morris, Toledo	Carll S. Mundy, Paul M. Holmes, A. B. Brower
Wendell H. Bennett, Youngstown	Colin R. Clark, W. H. Bunn, A. B. Brower
John Noll, Jr., Youngstown	Colin R. Clark, W. H. Bunn, A. B. Brower
Lewis K. Reed, Youngstown	W. H. Bunn, Colin R. Clark, A. B. Brower
Charles H. Warnock, Youngstown	Colin R. Clark, W. H. Bunn, A. B. Brower
Oklahoma	
James William Finch, Hobart	H. K. Speed, Arthur W. White, Lea A. Riely
Richard Michael Burke, Sulphur	Frank L. Jennings, E. S. Mariette, Lea A. Riely
Samuel Goodman, Tulsa	Russell C. Pigford, C. J. Fishman, Lea A. Riely
Oregon	
Irvin Reginald Fox, Eugene	F. A. Willius, A. H. Ross, T. Homer Coffen
Fred Nathan Miller, Eugene	A. H. Ross, John H. Fitzgibbon, T. Homer Coffen
Pennsylvania	
Alfred Winfield Dubbs, Allentown	Thomas Klein, Henry I. Klopp, Edward L. Bortz
Abraham Max Balter, Aspinwall	H. M. Margolis, Milton Goldsmith, R. R. Snowden
William Freas Confair, Benton	William Devitt, J. Allen Jackson, Edward L. Bortz
Frederick Otto Zillessen, Easton	John Edgar Fretz, L. G. Rowntree, Edward L. Bortz
Robert Deming Donaldson, Kane	George J. Kastlin, Clement R. Jones, R. R. Snowden
Clara L. Davis, Lansdowne	Thomas Fitz-Hugh, Jr., Frieda Baumann, Edward L. Bortz
Henry Joseph Tumen, Philadelphia	H. L. Bockus, H. L. Jameson, Edward L. Bortz
Ralph Charles Hoyt, Reading	John R. Spannuth, E. D. Funk, Edward L. Bortz

Candidates	*Sponsors*
Clair Grove Spangler, Reading	William S. Bertolet, John R. Spannuth, Edward L. Bortz
Marshall Graham, Washington	L. D. Sargent, G. W. Ramsey, E. Bosworth McCready, R. R. Snowden
South Carolina	
Allen Izard Josey, Columbia	J. Heyward Gibbes, O. B. Mayer, Kenneth M. Lynch
Tennessee	
Carl Adam Hartung, Chattanooga	James L. Bibb, Leopold Shumacker, J. O. Manier
Marvin Brown Corlette, Nashville	John B. Youmans, W. S. Leathers, J. O. Manier
Texas	
Max Erwin Suehs, Beaumont	L. T. Pruit, V. M. Longmire, M. D. Levy
Cecil Overton Patterson, Dallas	C. M. Grigsby, H. M. Winans, M. D. Levy
William Shelton Barcus, Fort Worth	Will S. Horn, May Owen, C. T. Stone, M. D. Levy
William Ladelle Howell, Fort Worth	Will S. Horn, C. O. Terrell, C. T. Stone, M.D. Levy
Edward Albert Wilkerson, Houston	M. D. Levy, LeRoy B. Duggan, C. T. Stone
Daniel Davis Warren, Waco	Joe Kopecky, J. H. Musser, M. D. Levy
Virginia	
William Riely Jordan, Richmond	Paul D. Camp, Dean B. Cole, J. Morrison Hutcheson
Walter Lewis Nalls, Richmond	Dean B. Cole, R. Finley Gayle, Jr., J. Morrison Hutcheson
West Virginia	
Alfred Spates Brady, Jr., Charleston	John Wm. Moore, A. A. Shawkey, Walter E. Vest
George Francis Evans, Clarksburg	G. R. Maxwell, Edward J. Van Liere, Walter E. Vest
Wisconsin	
Adolph Matthew Hutter, Fond du Lac	Wm. S. Middleton, Elmer L. Sevringhaus, Rock Sleyster
William Michael Jermain, Milwaukee	Joseph Lettenberger, Francis D. Murphy, Rock Sleyster
John Albert Schindler, Monroe	Wm. S. Midleton, Elmer L. Sevringhaus, Rock Sleyster
Einar Robert Daniels, Statesan	H. M. Coon, Wm. S. Middleton, Rock Sleyster
Harold Herman Fechtner, Wausau	Wm. S. Middleton, J. S. Evans, Rock Sleyster
Joseph John Furlong, Wauwatosa	Ralph A. Kinsella, Francis D. Murphy, Rock Sleyster
Puerto Rico	
Manuel Pavia-Fernandez, San Juan	R. Rodriguez Molina, O. Costa Mandry, Ramon M. Suarez

OBITUARY

Henry T. Von Deesten, 268 Palisade Avenue, Jersey City, New Jersey, died September 1, 1938, after a prolonged illness terminating in cardiac failure at the age of 59.

Dr. Von Deesten was born December 9, 1879. He received his preliminary education at the Hoboken High School, Hoboken, N. J. and the Hasbrunck Institute, Jersey City, N. J. He next entered the medical department of Columbia University, New York City, from which he graduated as M.D. in 1901.

He served as intern in the Bellevue Hospital, New York, N. Y., and the St. Mary's Hospital, Hoboken, New Jersey, during 1902 and 1903, and finally took postgraduate work in the University of Berlin, Berlin, Germany, for one year before beginning the practice of medicine in his native city.

Although quite feeble during his final years, Dr. Von Deesten continued to practice as best he could and was regarded by the local profession as an outstanding consultant because of his knowledge of internal medicine.

He held many hospital appointments during his medical career as follows: Formerly, Pathologist St. Mary's Hospital, Hoboken, New Jersey; Assistant Neurologist, Polyclinic Hospital, New York City. Visiting Physician, Christ Hospital, Jersey City, N. J. and St. Mary's Hospital, Hoboken, N. J. At the time of his death, he was Consulting Physician, Christ and St. Mary's Hospitals, Hoboken, N. J. and the Bayonne Hospital and Dispensary, Bayonne, New Jersey.

He was a member of the New York Academy of Medicine, the New Jersey State Medical Society, the American Medical Association, The Jersey City Practitioners Club, Jersey City, N. J., and a Fellow of the American College of Physicians since 1920.

Dr. Von Deesten's grit and stamina to carry on after he had been stricken down with hypertensive cardiovascular disease—the bane of the medical profession—exemplifies that intangible something which makes the medical man wholly disregard himself and think only of those whose lives are entrusted to his care. It is a lesson well worth any one's while to copy and a degree of sacrifice seldom seen except in our noble profession.

The community, the profession and his bereaved family have incurred an irreparable loss.

CLARENCE L. ANDREWS, M.D., F.A.C.P.,
Governor for New Jersey

PROGRAM

TWENTY-THIRD ANNUAL SESSION AMERICAN COLLEGE OF PHYSICIANS NEW ORLEANS, LA.

March 27–31, 1939

GENERAL SESSIONS AND LECTURES

William J. Kerr, President

NEW ORLEANS COMMITTEE ON ARRANGEMENTS

John H. Musser, General Chairman

P. H. Jones — Robert Bernhard
Allan Eustis — John Lanford
Edgar Hull — Randolph Lyons

COMMITTEE ON CLINICS AND DEMONSTRATIONS

P. H. Jones, Chairman

O. W. Bethea — W. L. Smith
J. M. Perret — C. S. Holbrook
W. R. Wirth

COMMITTEE ON TRANSPORTATION

Edgar Hull, Chairman

L. A. Monte — G. R. Williamson
R. H. Bayley

COMMITTEE ON ENTERTAINMENT

Robert Bernhard, Chairman

Anees Mogabgab — Ben Heninger
D. N. Silverman — Grace Goldsmith

COMMITTEE ON AUDITORIUM

Allan Eustis, Chairman

C. Tripoli — G. M. Decherd

COMMITTEE ON PUBLICITY

John Lanford, Chairman

M. E. Bass — Clyde Brooks
C. J. Bloom — Maud Loeber
C. W. Duval

COMMITTEE ON ROUND TABLES

Randolph Lyons, Chairman

C. C. Bass — J. M. Bamber
J. C. Cole

LADIES ENTERTAINMENT COMMITTEE

Mrs. C. Grenes Cole, Chairman

GENERAL INFORMATION

New Orleans Headquarters

Municipal Auditorium—General Headquarters
Roosevelt Hotel—General Hotel Headquarters
Jung Hotel—Convocation Headquarters

The New Orleans Municipal Auditorium will be general headquarters for registration, exhibits, general sessions, round tables, dry clinics and special lectures.

The Roosevelt Hotel will be headquarters for Officers, Regents, Governors and members of the College; also headquarters for the Ladies Entertainment Committee and the Annual Banquet.

The Jung Hotel will be the headquarters for the Convocation and President's Reception.

List of New Orleans Hotels	Blocks from Auditorium	Rates per day	
		Single Room with bath	Double Room with bath
ROOSEVELT HOTEL	7	$3.50–6.00	$4.50–8.00
JUNG HOTEL	7	3.00–4.00	5.00–8.00
De Soto Hotel	12	3.00–5.00	5.00–8.00
La Salle Hotel	5		4.00–5.00
Lafayette Hotel	16	2.50–3.00	3.50–5.00
Monteleone Hotel	8	3.00–4.00	5.00–8.00
New Orleans Hotel	6	3.00	4.00–6.00
St. Charles Hotel	11	3.00–5.00	5.00–8.00
Pontchartrain Hotel (Apartments)	31		8.00 up

Members should make reservations directly with hotels of their choice. Mention the Convention of the American College of Physicians, for rates above quoted are, in some instances, only for this occasion.

WHO MAY REGISTER—

(*a*) All members of the American College of Physicians in good standing for 1939 (dues, if not paid previously, may be paid at the Registration Bureau).

(*b*) All newly elected members.

(*c*) Members of the Orleans Parish Medical Society, without registration fee, upon presentation of their 1939 membership cards.

(*d*) Medical students pursuing courses at Tulane University of Louisiana School of Medicine and Louisiana State University Medical Center, without registration fee, upon presentation of matriculation cards, or other evidence of registration at these institutions; exhibits, morning lectures, dry clinics and general sessions.

(*e*) House Officers of the hospitals participating in the program, without registration fee, upon presentation of proper identification; exhibits, morning lectures, dry clinics and general sessions.

(*f*) Members of the Medical Corps of the Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials.

(*g*) Qualified physicians who may wish to attend this Session as visitors. Such physician shall pay a registration fee of $12.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee.

REGISTRATION BUREAU—Temporary Registration Bureau will be open at the Municipal Auditorium on Sunday afternoon and evening, March 26. The permanent Registration Bureau at the Auditorium will be open daily, 8:30 a.m. to 6:00 p.m., Monday to Friday, March 27–31.

REGISTRATION BLANKS FOR ALL CLINICS, DEMONSTRATIONS AND ROUND TABLE CONFERENCES will be sent to members of the College with the formal program. Guests will secure registration blanks at the Registration Bureau during the Session.

BULLETIN BOARDS FOR SPECIAL ANNOUNCEMENTS will be located in the lobby of the Roosevelt Hotel and near the Registration Bureau at the Municipal Auditorium.

TRANSPORTATION—On account of nationwide reductions in railroad fares, there are no convention rates any longer in effect. In many instances, however, reduced round trip tickets are in effect from certain localities. Members should consult their local ticket agents.

Special train from the East and Midwest—A special train will be operated from New York to New Orleans by way of Cincinnati over the Baltimore & Ohio and Louisville & Nashville Railroads, with special cars added from Pittsburgh, Detroit, Cleveland, Cincinnati and other points. A special train will be operated on the return journey from New Orleans to New York by way of the West Point route, Louisville & Nashville, Southern Railway and Pennsylvania Railroad. Special cars will also be operated by way of the Louisville & Nashville Railroad back to Cincinnati. These schedules have been arranged for the convenience of members and the best possible service is promised. Diverse routes will afford a more interesting journey. A special time-table will accompany the formal program later to be distributed to members.

GOING JOURNEY

Connections from New England

Saturday, March 25

	E.S.T.
Lv. Boston, Mass.	7.30 a.m.
Lv. Springfield, Mass.	9.25 a.m.
Lv. Hartford, Conn.	10.00 a.m.
Ar. New York	12.40 p.m.

Saturday, March 25

Lv. New York, 42nd St. Station	2.55 p.m.
Lv. New York, 33rd St. Station	2.57 p.m.
Lv. Jersey City ..... B&O RR "DIPLOMAT"	3.42 p.m.
Lv. Newark (Motor Connection)	3.35 p.m.
Lv. Elizabeth, N. J.	3.57 p.m.
Lv. West Trenton *	4.43 p.m.
* Special stop will be made for members to entrain.	
Lv. Philadelphia	5.28 p.m.
Lv. Chester, Pa.	5.44 p.m.
Lv. Wilmington, Del.	6.01 p.m.
Lv. Baltimore, Md. (Mt. Royal Sta.)	7.18 p.m.
Lv. Baltimore, Md. (Camden Sta.)	7.25 p.m.
Lv. Washington, D. C. (Union Sta.)	8.30 p.m.
Lv. Silver Spring, Md.	8.44 p.m.
Lv. Martinsburg, W. Va.	10.08 p.m.
Lv. Keyser, W. Va.	11.54 p.m.

Sunday, March 26

Lv. Chillicothe, Ohio	7.40 a.m.
Lv. Oakley, Ohio	9.29 a.m.

		E.S.T.
Ar. Cincinnati, Ohio (Union Sta.)		9.50 a.m.
Lv. Cincinnati	LOUISVILLE & NASHVILLE RR.	10.00 a.m.
Lv. Louisville, Ky.	LOUISVILLE & NASHVILLE RR "8"	12.22 p.m.
Lv. Nashville, Tenn.		4.45 p.m.
Lv. Birmingham		9.25 p.m.

Monday, March 27

Ar. New Orleans	LOUISVILLE & NASHVILLE RR.	7.55 a.m.

Connecting Trains

Saturday, March 25

Lv. Pittsburgh, Pa.	BALTIMORE & OHIO RR.	9.00 p.m.
Lv. Washington, Pa.		10.03 p.m.
Lv. Wheeling, W. Va.		11.20 p.m.

Sunday, March 26

Ar. Cincinnati, Union Terminal		6.40 a.m.

Saturday, March 25

Lv. Detroit, Mich.	BALTIMORE & OHIO RR.	*11.00 p.m.
Lv. Toledo, Ohio		*1.00 a.m.

* Sleeper ready at 9.30 p.m.

Sunday, March 26

Ar. Cincinnati (Union Sta.)		6.55 a.m.

Saturday, March 25

Lv. Cleveland, Ohio	BIG FOUR ROUTE.	*12.15 a.m.

* Car open at 9.30 p.m.

Sunday, March 26

Ar. Cincinnati, Ohio, Union Terminal		7.00 a.m.

Saturday, March 25

Lv. Buffalo, N. Y.	NEW YORK CENTRAL RR.	11.45 p.m.

Sunday, March 26

Ar. Cincinnati, Union Terminal		8.30 a.m.

Saturday, March 25

Lv. Syracuse, N. Y.	NEW YORK CENTRAL RR.	8.57 p.m.
Lv. Rochester, N. Y.		10.30 p.m.

Sunday, March 26

Ar. Cincinnati		8.30 a.m.

Sunday, March 26

Lv. Indianapolis, Ind.	PENNSYLVANIA RR.	8.35 a.m.
Ar. Louisville, Ky.		11.45 a.m.

Saturday, March 25

		E.S.T.
Lv. Chicago	BIG FOUR ROUTE	11.45 p.m.

Sunday, March 26

Ar. Cincinnati, Union Terminal		7.55 a.m.

Note

Delegates desiring to move direct to New Orleans may use ILLINOIS CENTRAL RR (Panama Limited) leaving Chicago 1.00 p.m., Sunday, March 26, arriving in New Orleans 9.00 a.m., March 27. A service charge of $5.00 applies on this train.

Sunday, March 26

Lv. St. Louis	ILLINOIS CENTRAL RR	4.45 p.m.

Monday, March 27

Ar. New Orleans, La.		9.00 a.m.

RETURNING JOURNEY

At the close of the meeting, through cars will be operated to the various cities

Friday, March 31

Lv. New Orleans, La.	WEST POINT ROUTE	10.15 p.m.

Saturday, April 1

Ar. Montgomery, Ala.	L&N RR	7.55 a.m.
Ar. Atlanta, Ga.	AW&P RR	12.45 p.m.

Sunday, April 2

Ar. Washington	SOUTHERN RY	*4.50 a.m.
Ar. Baltimore	PRR	5.48 a.m.
Ar. Wilmington, Del.	PRR	6.49 a.m.
Ar. Philadelphia, Pa.	PRR	7.22 a.m.
Ar. Newark, N. J.	PRR	8.58 a.m.
Ar. New York, N. Y.	PRR	9.55 a.m.

The Committee on Transportation will issue full data concerning local transportation at the meeting.

THE GENERAL BUSINESS MEETING OF THE COLLEGE will be held at 4:45 p.m., Thursday, March 30, immediately following the general scientific program of the afternoon. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors, the reports of the Treasurer and of the Executive Secretary, and the induction to office of the new President, Dr. O. H. Perry Pepper, Philadelphia, Pa.

BOARD AND COMMITTEE MEETINGS—The following meetings are scheduled as indicated. Special meetings will be announced and posted.

A *combined dinner* of the Board of Regents and of the Board of Governors will be given at the Roosevelt Hotel, Sunday evening, March 26, at seven o'clock.

COMMITTEE ON CREDENTIALS

Sunday, March 26, 9:00 a.m.....Municipal Auditorium, Executive Secretary's Office

* Sleeper may be occupied until 8.00 a.m.

BOARD OF REGENTS

Municipal Auditorium, 1st Floor, First Aid Room
Sunday, March 26, 2:30 p.m.
Tuesday, March 28, 12:00 m.*
Friday, March 31, 12:00 m.*

BOARD OF GOVERNORS

Municipal Auditorium, 2nd Floor, Memorial Hall (St. Peter St.)
Monday, March 27, 5:00 p.m.
Wednesday, March 29, 12:00 m.*

SPECIAL FEATURES

Monday, March 27, 1939

THE ANNUAL SMOKER will be held in the Ball Room of the Roosevelt Hotel on Monday, following the evening meeting, at 10:30 o'clock. The program will consist of a series of vaudeville acts mostly by professionals. The performers of the Blue Room (Roosevelt Hotel), the best night club of the City, will put on their show, in addition to which there will be a considerable number of local performers.

The Entertainment Committee reports that the program will go from the one extreme of the rendition of negro spirituals to the other extreme of staging a fan dance. Light refreshments and beer will be served. Admission will be limited to those displaying the official registration badge. Fellows and Associates, local and guest physicians, and the technical exhibitors are invited to attend the Smoker as guests of the College.

Wednesday, March 29, 1939

CONVOCATION OF THE COLLEGE—8:30 p.m., Tulane Room, Jung Hotel. All Masters and Fellows of the College, and those to be received into Fellowship, should be present. Newly elected Fellows who have not yet been received into Fellowship are requested to assemble in the Lounge, mezzanine floor, just outside the Tulane Room, at 7:45 o'clock, preparatory to the formation of the procession. They will occupy especially reserved seats in the central section of the Tulane Room, to which they will be conducted by the Convocation Marshal promptly at 8:30 o'clock. It is suggested that all appear in evening dress.

The Convocation is open to all physicians and their families generally. A cordial invitation is also issued to such of the general public as may be interested.

The Convocation Ceremony will include an address by the President of the College, the presentation of newly elected Fellows, the award of the John Phillips Memorial Medal, the announcement of the Research Fellows of the College for 1939 and the presentation of the Annual Lecture.

The Presidential Reception, with dancing, will follow after a fifteen-minute intermission at the termination of the exercises. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception.

Thursday, March 30, 1939

THE ANNUAL BANQUET OF THE COLLEGE will be held in the Grand Ballroom of the Roosevelt Hotel on Thursday evening at eight o'clock. Dr. John H. Musser, General Chairman of the Twenty-third Annual Session of the College, will be the Toastmaster. Two interesting addresses will be delivered: Mrs. E. M. Gilmer, widely known as "Dorothy Dix," will tell about her experiences and letters during

* Buffet luncheon served.

her long career as a newspaper columnist; Mr. Lyle Saxon, an historian of note, who has written such books as "Fabulous New Orleans," "Lafitte, the Pirate," and several others nationally known, will be the second speaker, and his subject will be announced later.

All members of the College, physicians of New Orleans and visitors attending the Session, with their families, are cordially invited. Tickets should be purchased at the registration bureau by Wednesday afternoon—price, $4.00.

PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The Headquarters of the Women's Entertainment Committee will be located at the Roosevelt Hotel. While all visiting ladies are welcome to visit the Auditorium and inspect the exhibits, it is thought that a much more convenient and attractive headquarters for them is available at the Roosevelt Hotel. Each visitor will receive a program of the activities planned for their entertainment by the Women's Entertainment Committee. A secretary will be in charge to assist visitors in arranging their entertainment program. Visiting women are requested to register on arrival and make reservations for the events announced in the program. Additional literature containing information regarding theaters, restaurants and places of entertainment will be available at the registration desk.

The sole purpose of the Women's Entertainment Committee is to assist the visiting ladies in securing the greatest possible enjoyment and entertainment from their visit to New Orleans. It is hoped that as a result of the activities of this Committee, visitors will carry away with them the most pleasant memories of their stay. It would greatly facilitate the work of the Committee if each Fellow or Associate who will be attended by ladies will return the card accompanying the program as promptly as possible.

Monday, March 27, 1939

Morning: Registration, Roosevelt Hotel.
Afternoon: 4:00 to 5:30 p.m. Tea at the Orleans Club.
Evening: Program (negro spirituals) at the Hutchinson Memorial.

Tuesday, March 28, 1939

Morning: Free for shopping, or to stroll down Royal Street to visit the antique shops.
Afternoon: 12:30 p.m. Luncheon and sight-seeing tour of the Vieux Carre; Ladies of the Woman's Auxiliary of the Orleans Parish Medical Society will act as guides. Tea will be served after the sight-seeing trip at the home of Mrs. Isaac I. Lemann in the French Quarter.
Evening: Bus ride through New Orleans and to the shores of Lake Pontchartrain, returning for coffee at the old French Market. Tickets, $1.60.

Wednesday, March 29, 1939

Morning: 8:30 a.m. Bus trip to old plantation homes of Louisiana—an all-day trip, with luncheon served en route. Return to Roosevelt Hotel at 5:00 p.m. Fare, $2.75.
Evening: 8:30 p.m. Convocation, President's Reception and Dance at the Jung Hotel.

Thursday, March 30, 1939

Morning: 11:00 a.m. French Breakfast at the New Orleans Country Club (this may later be changed to a trip through the New Orleans parks, with a picnic luncheon served under the old dueling oaks in City Park).
Afternoon: Three-hour boat ride on the Mississippi River. Fare, $1.50.
Evening: 8:00 p.m. .Annual Banquet of the College, Roosevelt Hotel.

VISIT TO LEPROSARIUM

An invitation has been extended by Dr. H. E. Hasseltine, of the U. S. Public Health Service, to visit the Public Health Service's Leprosarium at Carville, La., on Saturday, April 1. This is one of the most remarkable institutions of its kind in the world, and will well repay the time required to make this trip, which is some ninety miles above New Orleans on the Mississippi River.

Fellows who wish to make the trip to Carville should sign up at the Registration Desk. Transportation will be provided at a cost dependent upon the number who will go to Carville. If possible, members are asked to indicate their desire to visit the Leprosarium when they register, in order that Dr. Hasseltine may be notified twenty-four hours ahead of time of the number who anticipate attending the clinics and demonstrations, and probably the luncheon which will be served.

SPECIAL FEATURES

Points of Interest

The following places will be of interest to visiting physicians and their wives to visit some time during the course of the Annual Session:

THE NEW CHARITY HOSPITAL—This structure, which will accommodate 2,400 patients, will be completed, but probably not occupied by the last of March. The hospital will represent the best in everything which has to do with hospital administration and the care of the sick.

TULANE UNIVERSITY OF LOUISIANA MEDICAL SCHOOL; Hutchinson Memorial and the Richardson Memorial, and the Hall of Science, will be open for visitors. The Hutchinson Memorial is only three blocks from the Roosevelt Hotel. In it may be viewed the Library containing the Matas Historical Exhibit, the exhibit of the Department of Tropical Medicine, and also the very interesting method of conducting an outpatient department primarily for the purpose of demonstrating to the students the proper office care of the sick individual.

THE LOUISIANA STATE UNIVERSITY MEDICAL CENTER—On the grounds of the Charity Hospital. This new and modern building contains a variety of medical exhibits, which should be of interest.

TULANE UNIVERSITY—In addition to the usual things that are to be found in a university, particularly to be emphasized, is the splendid Maya collection of Indian relics of pre-historic days, brought from Central America by various Tulane expeditions.

THE FRENCH QUARTER—Here may be seen The Cabildo, St. Louis Cathedral, Jackson Square, the Pontalba Buildings (incidentally, the first apartment houses in the United States), Le Petit Theater du Vieux Carre and the Patio where Lafitte was supposed to keep his booty.

THE DELGADO MUSEUM, the old dueling oaks, extensive playgrounds and other features may be viewed in the City Park.

Other outstanding interesting features of New Orleans include: the smallest shrine in the country, St. Roch's; the cemeteries with the bodies interred above ground; the Southern Yacht Club on Lake Pontchartrain; the new Municipal Airport, the largest in the country; the Levees.

POST-CONVENTION CRUISES AND TOURS

(Consult Advertising Section and News Notes Section of this Issue)

THE EXPOSITION AND TECHNICAL EXHIBIT will be located on the main floor of the New Orleans Municipal Auditorium.

By official action of the Board of Regents of the College, the technical exhibits have been raised to a higher level of excellence through the elimination of all irrelevant and non-scientific entries. The rules adopted governing this Exhibit are as follows:

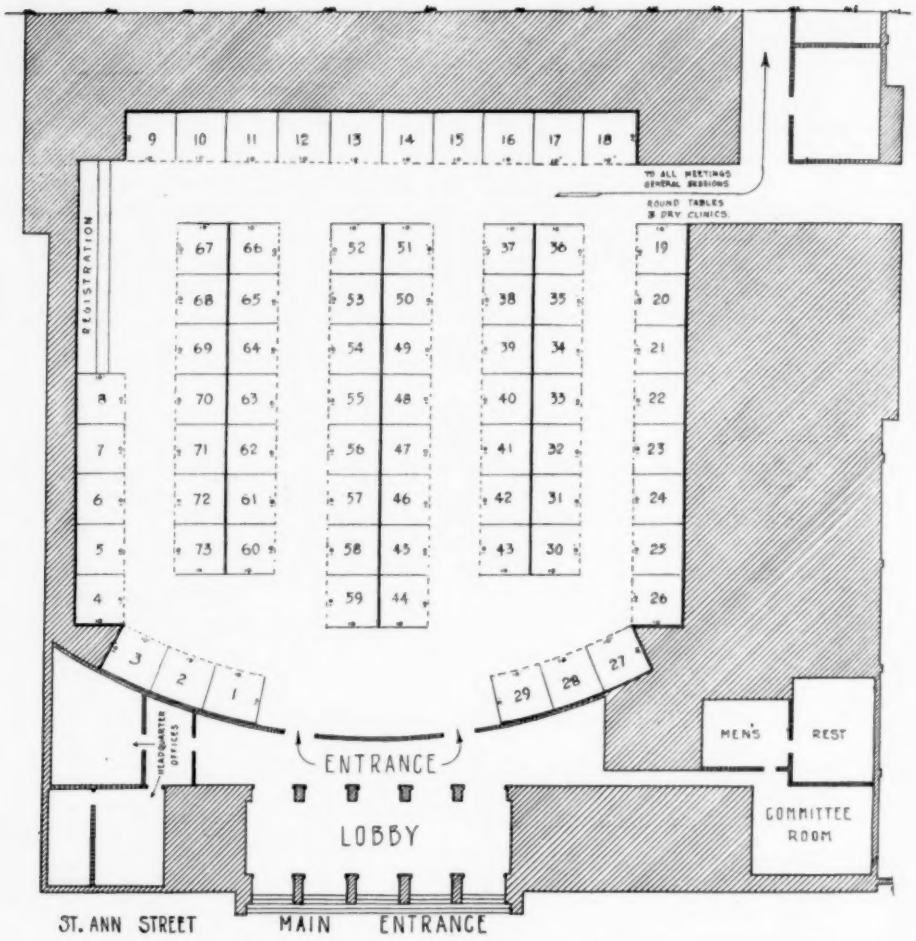
(1) Exhibitors shall be admitted on invitation only;
(2) The initial approved "Invitation List" shall be made up by the Committee and the Executive Secretary. Both the firm and the product must be approved. Preference shall be given to exhibits of a scientific nature, such as pharmaceuticals, equipment and medical books;
(3) Additions to the initial approved "Invitation List" may be made by the Committee after application by firms, with the requirement that they submit complete literature concerning their products and their organization;
(4) The "Invitation List" may be revised annually on the recommendation of the Committee.

The Committee on Exhibits has thoroughly investigated each exhibit before extending invitations. The number of exhibitors has been limited, and it is hoped that members and visiting physicians will find these exhibits more interesting and more beneficial. The exhibits will be particularly representative of the interests of Internal Medicine and its allied specialties, and will include medical literature, pharmaceutical products, apparatus and appliances, specialized physicians' furniture and many other items of special interest. Each doctor is urged to visit each of the booths, for the educational value of these exhibits adds greatly to the interesting features of the meeting. Furthermore, the exhibitors themselves solicit the courtesy of the inspection of their displays, on which they have spent much time, thought and money. Special intermissions in the general program have been arranged, providing additional time for inspection of exhibits.

LIST OF EXHIBITORS

(Not yet complete)

	Space
Allison Company, W. D., Indianapolis, Ind.	48
Appleton-Century Company, D., New York, N. Y.	19
Ayerst, McKenna & Harrison (United States) Limited, Montreal, Que.	47
Baum Co., Inc., W. A., New York, N. Y.	8
Becton, Dickinson & Co., Rutherford, N. J.	72–73
Bilhuber-Knoll Corp., Orange, N. J.	30–31
Burroughs Wellcome & Co. (U. S. A.) Inc., New York, N. Y.	2
Cambridge Instrument Co., Inc., New York, N. Y.	26
Cameron Surgical Specialty Company, Chicago, Ill.	23–36
Collins, Inc., Warren E., Boston, Mass.	27
Davies, Rose & Company, Limited, Boston, Mass.	24
Davis Company, F. A., Philadelphia, Pa.	33
Devereux Schools, Inc., Berwyn, Pa.	56
Doak Company, The, Cleveland, Ohio	71
General Electric X-Ray Corporation, Chicago, Ill.	13–14–15
Gerber Products Company, Fremont, Mich.	42
Glen Springs, The, Watkins Glen, N. Y.	61
Gradwohl School of Laboratory Technique, St. Louis, Mo.	7
Heinz Co., H. J., Pittsburgh, Pa.	32
Hoeber, Inc., Paul B., New York, N. Y.	37
Jones Metabolism Equipment Co., Chicago, Ill.	3
Kalak Water Co., New York, N. Y.	9



PLAN OF TECHNICAL EXHIBIT, NEW ORLEANS MUNICIPAL AUDITORIUM

LaMotte Chemical Products Company, Baltimore, Md. 20
Lea & Febiger, Philadelphia, Pa. 59
Lederle Laboratories, Inc., New York, N. Y. 16–17–18
Lilly & Co., Eli, Indianapolis, Ind. 67–68–69
Lippincott Company, J. B., Philadelphia, Pa. 60
Macmillan Company, The, New York, N. Y. 12
Majors Co., J. A., New Orleans, La. 1
Mead Johnson & Company, Inc., Evansville, Ind. 10–11
Medical Bureau, The, Chicago, Ill. 43
Merck & Co. Inc., Rahway, N. J. 21–22
Merrell Company, The Wm. S., Cincinnati, Ohio 38–39
Mosby Company, The C. V., St. Louis, Mo. 70
Muller Laboratories, The, Baltimore, Md. 25
Oxford University Press, New York, N. Y. 28
Petrolagar Laboratories, Inc., Chicago, Ill. 52
Ralston Purina Co., St. Louis, Mo. 46

Riedel-de Haen, Inc., New York, N. Y. 34
Sanborn Company, Cambridge, Mass. 35
Saunders Company, W. B., Philadelphia, Pa. 1
Schering Corporation, Bloomfield, N. J. 66
Scientific Sugars Co., Columbus, Ind. 62
S. M. A. Corporation, Chicago, Ill. 53
Smith, Kline & French Laboratories, Philadelphia, Pa. 44–45
Spicer and Company, Glendale, Calif. 4
Squibb & Sons, E. R., New York, N. Y. 40–41
Stearns & Company, Frederick, Detroit, Mich. 29
Taylor Instrument Companies, Rochester, N. Y. 49–50
Westinghouse X-Ray Co., Inc., Long Island City, N. Y. 5–6
Winthrop Chemical Company, Inc., New York, N. Y. 51
Wyeth & Bro., Inc., John, Philadelphia, Pa. 57–58

GENERAL SESSIONS PROGRAM

New Orleans Municipal Auditorium

FIRST GENERAL SESSION

Monday Afternoon, March 27, 1939

Presiding Officer

John H. Musser, New Orleans, La.

p.m.

2:30 Addresses of Welcome:
Responses to Addresses of Welcome.
William J. Kerr, President of the American College of Physicians.

3:15 The Postgraduate Portion of Medical Education.
C. Sidney Burwell, Dean of the Faculty of Medicine and Research Professor of Clinical Medicine, Harvard University Medical School, Boston, Mass.

3:45 INTERMISSION.

4:15 Some Professional and Social Trends in American Medicine.
Irvin Abell, President of the American Medical Association, Louisville, Ky. (By invitation.)

4:45 The Limitations of Government in Medicine: The San Francisco Experience.
J. C. Geiger, Director of Public Health, City and County of San Francisco, San Francisco, Calif.,
J. P. Gray, Director of Public Welfare, City and County of San Francisco, San Francisco, Calif. (By invitation) and
A. E. Larsen, Director, Central Medical Bureau, State Relief Administration in San Francisco, Calif. (By invitation.)

5:15 ADJOURNMENT.

SECOND GENERAL SESSION

Monday Evening, March 27, 1939

Presiding Officer

O. H. Perry Pepper, Philadelphia, Pa.

p.m.

8:00 The Prognosis of Bacterial Endocarditis. End Results in 129 Cases.
Joseph A. Capps, Professor of Clinical Medicine, University of Chicago; Attending Physician, St. Luke's Hospital; Chicago, Ill.

OUTLINE OF NEW ORLEANS SESSION

Municipal Auditorium events are indicated in **bold type**

TIME	MONDAY	TUESDAY		WEDNESDAY		THURSDAY		FRIDAY	
9:00 a.m. to 12:00 m.	Morning free **Registration, Exhibits, etc.**	9 to 12 Hospital Clinics	**10 to 12 Lectures**	**9 to 11 Dry Clinics**	**10 to 12 Round Tables**	9 to 12 Hospital Clinics	**10 to 12 Lectures**	**9 to 11 Dry Clinics**	**10 to 12 Round Tables**
12:00 m. to 2:00 p.m.	Luncheon	Luncheon		Luncheon		Luncheon		Luncheon	
2:00 p.m. to 5:00 p.m.	**1st General Session**	**3rd General Session**		**4th General Session**		**5th General Session General Business Meeting**		**6th General Session**	
5:00 p.m. to 8:00 p.m.	Dinner	Dinner		Dinner					
8:00 p.m. to 10:00 p.m.	**2nd General Session**			Pre-Convocation Assembly 7:45 p.m. Convocation 8:30 p.m.		ANNUAL BANQUET			
10:00 p.m. to 12:00 p.m.	Annual Smoker and Social Evening			Followed by President's Reception about 10:30 p.m.					

8:20 Neoprontosil (Oral) in the Treatment of Chronic Ulcerative Colitis.
Alex E. Brown, Associate in Medicine, Mayo Clinic, and Assistant Professor of Medicine, The Mayo Foundation; Rochester, Minn.,
Wallace E. Herrell, Associate in Medicine, Mayo Clinic, and Instructor in Medicine, The Mayo Foundation; Rochester, Minn., and
J. Arnold Bargen, Associate in Medicine, Mayo Clinic, and Associate Professor of Medicine, The Mayo Foundation; Rochester, Minn.

8:35 The Experimental and Clinical Use of Pyridine Derivatives of Sulphanilamide in the Treatment of Bacterial Infections.
Perrin H. Long, Associate Professor of Medicine, Johns Hopkins University School of Medicine; Associate Physician, Johns Hopkins Hospital; Baltimore, Md. (By invitation); and
Eleanor A. Bliss, Fellow in Medicine, Johns Hopkins University School of Medicine, Baltimore, Md. (By invitation.)

8:55 Culture of Human Marrow: Studies of the Effects of Roentgen-Rays on Normal and Malignant Cells.
Edwin E. Osgood, Assistant Professor of Medicine, University of Oregon Medical School, Portland, Ore. (By invitation.)

9:10 Topic and Speaker to be announced later.

9:40 The Choice Between Ovarian and Pituitary Therapy for Menstrual Irregularity.
Elmer L. Sevringhaus, Professor of Medicine, University of Wisconsin Medical School; Associate Physician, Wisconsin General Hospital; Madison, Wis.

10:00 ADJOURNMENT.

10:30 o'Clock

SMOKER

Ball Room, Roosevelt Hotel

An interesting and amusing program has been arranged. Admission by registration badge.

THIRD GENERAL SESSION

Tuesday Afternoon, March 28, 1939

Presiding Officer

William D. Stroud, Philadelphia, Pa.

p.m.

2:00 Recent Advances in the Understanding of the Causes of Hypertensive States.
Tinsley R. Harrison, Associate Professor of Internal Medicine, Vanderbilt University School of Medicine, Nashville, Tenn. (By invitation);
Arthur Grollman, Associate Professor of Pharmacology, Johns Hopkins University School of Medicine, Baltimore, Md. (By invitation.); and
John R. Williams, Jr., Research Assistant, Vanderbilt University Hospital, Nashville, Tenn. (By invitation.)

2:20 Gravidarteriasis.
Francisco deP. Miranda, Professor of Clinical Medicine, Universidad Nacional Facultad de Medicina, Mexico, D. F.

2:40 The Plasma Lipoids in Arteriosclerosis Obliterans.
Nelson W. Barker, Consultant in Department of Medicine, Mayo Clinic; Associate Professor of Medicine, The Mayo Foundation; Rochester Minn.

2:55 The Management of Early Essential Hypertension.
Henry M. Thomas, Jr., Visiting Physician, Johns Hopkins Hospital, Baltimore, Md.

3:10 Five Years Experience with Mortality from Acute Coronary Occlusion in Philadelphia (1932–1937).
O. F. Hedley, Passed Assistant Surgeon, U. S. Public Health Service, Philadelphia, Pa.

3:25 Roentgen Procedures Useful in Cardiac Diagnosis.
Fred J. Hodges, Professor of Roentgenology, University of Michigan Medical School, Ann Arbor, Mich. (By invitation.)

3:45 INTERMISSION.

4:15 The Clinical Value of Visualization of the Chambers of the Heart, the Pulmonary Circulation and the Great Vessels.
George P. Robb, Assistant in Clinical Medicine, New York University College of Medicine; Clinical Assistant Visiting Physician, Bellevue Hospital; New York, N. Y., and
Israel Steinberg, Instructor in Medicine, New York University College of Medicine; Assistant Visiting Physician, Bellevue Hospital; New York, N. Y.

4:30 The Excretion Time of Quinidine from the Blood and the Heart Muscle.
Samuel A. Weisman, Assistant Professor of Medicine, University of Minnesota Medical School, Minneapolis, Minn.

4:45 Electrocardiographic Findings Following Carotid Sinus Stimulation.
W. Kendrick Purks, Director, Department of Internal Medicine, Vicksburg Hospital, Inc., and Vicksburg Clinic; Medical Consultant, Mississippi State Hospital; Vicksburg, Miss.

5:00 Studies in the Mechanism of Cardiac Hypertrophy.
George R. Herrmann, Professor of Clinical Medicine, Department of Practice of Medicine, University of Texas, Galveston, Tex.

5:15 ADJOURNMENT.

FOURTH GENERAL SESSION

Wednesday Afternoon, March 29, 1939

Presiding Officer

David P. Barr, St. Louis, Mo.

p.m.

2:00 The Influence of Iron and Diet on the Blood in Pregnancy.
Frank H. Bethell, Assistant Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor, Mich. (By invitation.)

2:15 The Nutritional Significance of Nicotinic Acid.
C. A. Elvehjem, Professor of Biochemistry, University of Wisconsin, Madison, Wis. (By invitation.)

2:35 Recent Advances in the Treatment of Pellagra.
Tom Douglas Spies, Professor of Medicine, University of Cincinnati College of Medicine; Attending Physician, Cincinnati General Hospital; Cincinnati, Ohio. (By invitation.)

2:50 The Influence of Vitamin Deficiencies on Other Diseases.
John B. Youmans, Associate Professor of Medicine and Director of Postgraduate Instruction, Vanderbilt University School of Medicine; Visiting Physician and Chief of Clinic of Outpatient Service, Vanderbilt University Hospital; Nashville, Tenn.

3:05 Clinical Studies in Acidosis and Alkalosis.
Alexis F. Hartmann, Professor of Pediatrics, Washington University School of Medicine; Physician-in-Chief, St. Louis Children's Hospital; Pediatrician-in-Chief, St. Louis Maternity Hospital and Washington University Clinics; St. Louis, Mo. (By invitation.)

3:30 INTERMISSION.

4:00 Anaphylaxis and Allergy.
Carl A. Dragstedt, Professor of Pharmacology, Northwestern University Medical School, Chicago, Ill. (By invitation.)

4:30 Epidemic Syphilis: Its Recognition and Management by the Physician.
E. Gurney Clark, Instructor in Clinical Medicine, Vanderbilt University School of Medicine; Epidemiologist in the Syphilis Clinic and Associate Visiting Physician, Outpatient Service, Vanderbilt University Hospital; Nashville, Tenn. (By invitation.)

4:45 Human and Equine Encephalitis.
James P. Leake, Medical Director, U. S. Public Health Service; In Charge of the Office of Epidemiological Studies, Division of Infectious Diseases, National Institute of Health; Washington, D. C.

5:05 ADJOURNMENT.

ANNUAL CONVOCATION

Wednesday Evening, March 29, 1939

8:30 o'Clock

Tulane Room, Jung Hotel

All members of the profession and the general public are cordially invited. No special admission tickets will be required.

1. Address by the President of the College.
William J. Kerr.
2. Presentation of Newly-Elected Fellows and Recital of the Pledge.
George Morris Piersol, Secretary-General.
3. Presentation of John Phillips Memorial Medal for 1938–39.
4. Announcement of Research Fellows of the College for 1939.
5. Convocational Oration (title and speaker to be announced later).

President's Reception

The Reception and Dance will follow immediately after the program. Newly-inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception.

FIFTH GENERAL SESSION

Thursday Afternoon, March 30, 1939

Presiding Officer

Walter W. Palmer, New York, N. Y.

p.m.

2:00 Benign and Carcinomatous Gastric Ulcers: Their Relationship and Differentiation.
Walter L. Palmer, Associate Professor of Medicine, The School of Medicine of the Division of Biological Sciences, University of Chicago, Chicago, Ill. (By invitation.)

2:15 The Composition of Regenerated Liver Tissue.
B. O. Raulston, Professor of Medicine, University of Southern California School of Medicine, Los Angeles, Calif.

2:30 Hemolytic Jaundice: A Clinical Analysis of 28 Cases.
John C. Sharpe, Instructor in Medicine, University of Nebraska College of Medicine, Omaha, Nebr. (By invitation.)

2:45 A Study of the Therapeutic and Provocative Tests in Gout.
L. Maxwell Lockie, Associate in Medicine, University of Buffalo School of Medicine; Assistant Attending Physician, Outpatient Department, Buffalo General Hospital; Clinical Assistant, Inpatient Department, and Assistant Attending Physician, Outpatient Department, Children's Hospital; Buffalo, N. Y.

3:00 A Note on the Mechanism of Spontaneous Pneumothorax.
Louis Hamman, Associate Professor of Medicine, Johns Hopkins University School of Medicine; Visiting Physician, Johns Hopkins Hospital; Visiting Physician, Union Memorial Hospital; Baltimore, Md.

3:15 Specific Serotherapy and Chemotherapy of Pneumococcus Pneumonias.
Maxwell Finland, Assistant in Medicine, Harvard University Medical School; Assistant Physician, Thorndike Memorial Laboratory; Junior Visiting Physician, Boston City Hospital; Boston, Mass.

3:45 INTERMISSION.

4:15 Experimental and Clinical Observations Relating to the Management of Acute Bowel Obstructions.
Owen H. Wangensteen, Professor of Surgery, University of Minnesota Medical School; Surgeon-in-Chief, University Hospital; Minneapolis, Minn. (By invitation.)

4:45 ADJOURNMENT, to be followed by

ANNUAL BUSINESS MEETING

The Annual Business Meeting of the College will be held immediately after the last paper. All Masters and Fellows are urged to be present. Official reports will be made by the Treasurer and the Executive Secretary; new Officers, Regents and Governors will be elected, and the President-Elect, Dr. O. H. Perry Pepper, will be inducted into office.

Thursday Evening, 8:00 o'Clock

Grand Ballroom, Roosevelt Hotel

THE ANNUAL BANQUET OF THE COLLEGE

(Procure Tickets at the Registration Bureau)

Consult Special Banquet Program

SIXTH GENERAL SESSION

Friday Afternoon, March 31, 1939

Presiding Officer

Charles T. Stone, Galveston, Tex.

p.m.

2:00 Intersexuality or Pseudo-hermaphrodism.
A. C. Ivy, Nathan Smith Davis Professor of Physiology and Pharmacology, Northwestern University Medical School, Chicago, Ill.

2:20 The Use of Dihydrotachysterol in Hypoparathyroidism.
Homer P. Rush, Assistant Professor of Medicine, University of Oregon Medical School; Chief of Medical Service 3, Adult Hospital of the University of Oregon Medical School; Attending Physician, St. Vincent's Hospital; Attending Physician, Good Samaritan Hospital; Portland, Ore.

2:35 Chemical Specificity in Growth and Development.
Stanley P. Reimann, Director of The Lankenau Hospital Research Institute; Associate Professor of Surgical Pathology, Graduate School of Medicine. University of Pennsylvania; Philadelphia, Pa. (By invitation.)

2:55 The Relationship Between Function and Structure of the Thyroid in the Light of Colloid Measurements.
Eduard Uhlenhuth, Professor of Anatomy, University of Maryland School of Medicine, Baltimore, Md. (By invitation.)

3:25 INTERMISSION.

3:55 Relations Between Body Weight and Dosage of Drugs.
W. T. Dawson, Professor of Pharmacology, University of Texas School of Medicine; Pharmacologist, John Sealy Hospital; Galveston, Tex. (By invitation.)

4:25 Myotonia: Its Nature and Occurrence.
Abe Ravin, Instructor in Medicine, University of Colorado School of Medicine and Hospitals, Denver, Colo. (By invitation); and
James J. Waring, Professor of Medicine, University of Colorado School of Medicine and Hospitals, Denver, Colo.

4:40 Pharmacological Treatment in Schizophrenic Patients.
S. Katzenelbogen, Director of Laboratories and Research, St. Elizabeth's Hospital, Washington, D. C.;
Alexander Simon, Medical Officer, St. Elizabeth's Hospital, Washington, D. C. (By invitation);
Anna R. Coyne, Assistant Medical Officer, St. Elizabeth's Hospital, Washington, D. C. (By invitation); and
Charles E. Vigue, Junior Medical Officer, St. Elizabeth's Hospital, Washington, D. C. (By invitation.)

5:00 ADJOURNMENT.

PROGRAM OF MORNING LECTURES

New Orleans Municipal Auditorium

This course of Lectures has become a regular feature of the program. It is presented as an elective, in place of hospital clinics. The Lectures will not conflict with the General Sessions or with the Round Table Conferences. The Lectures are

scheduled only for Tuesday and Thursday mornings, from 10:00 a.m. to 12:00 m. in the main meeting room of the Auditorium.

The Lectures will be open to all members and guests of the College. Admission by regular registration badge.

Tuesday Morning, March 28, 1939

Presiding Officer

Henry M. Thomas, Jr., Baltimore, Md.

a.m.

10:00 A Study of Experimental Virus Infections in the Chick Embryo.
Ernest W. Goodpasture, Professor of Pathology, Vanderbilt University School of Medicine; Pathologist-in-Chief, Vanderbilt University Hospital; Nashville, Tenn. (By invitation.)

10:30 Epidemic Influenza: Studies in Clinical Epidemiology.
Thomas Francis, Jr., Professor of Bacteriology and Director of Laboratories, New York University College of Medicine; Assistant Visiting Physician, Willard Parker Hospital; Visiting Physician on Third (New York University) Medical Division, Bellevue Hospital; New York, N. Y. (By invitation.)

11:00 A Study of the Nature of Bacteremia in Experimental Pneumonia.
O. H. Robertson, Professor of Medicine, The School of Medicine of the Division of Biological Sciences, University of Chicago, Chicago, Ill. (By invitation);
Morton Hamburger, Jr., Research Assistant, Department of Medicine, The School of Medicine of the Division of Biological Sciences, University of Chicago, Chicago, Ill. (By invitation); and
Lucien A. Gregg, Research Assistant, Department of Medicine, The School of Medicine of the Division of Biological Sciences, University of Chicago, Chicago, Ill. (By invitation.)

11:30 Colored Motion Pictures of the Acute Exanthems.
Harry A. Towsley, Instructor, Department of Pediatrics and Infectious Diseases, University of Michigan Medical School, Ann Arbor, Mich. (By invitation.)

12:00 ADJOURNMENT.

Thursday Morning, March 30, 1939

Presiding Officer

William B. Breed, Boston, Mass.

a.m.

10:00 Suggested Revisions of Medical Pharmacology.
Paul D. Lamson, Professor of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tenn. (By invitation.)

10:30 Living with the Weather.
F. M. Pottenger, Clinical Professor of Medicine, University of Southern California School of Medicine; Medical Director, The Pottenger Sanatorium and Clinic for Diseases of the Chest; Monrovia, Calif.

11:00 An Unwritten Chapter in the Physiology of Aging.
A. J. Carlson, Professor of Physiology, University of Chicago, Chicago, Ill.

11:30 Newer Insulins.
Elliott P. Joslin, Medical Director, George F. Baker Clinic, New England Deaconess Hospital; Clinical Professor Emeritus, Harvard University Medical School; Boston, Mass.
12:00 ADJOURNMENT.

ROUND TABLE CONFERENCES

The Round Tables will be held Wednesday and Friday mornings, from 10:00 a.m. to 12:00 m. They will be conducted by outstanding authorities on the subjects assigned. There will be no conflict between the Round Tables and the program of Special Lectures and General Sessions. They will, however, somewhat overlap the program of Dry Clinics, and are offered partially as an elective for the Dry Clinics between 10:00 and 11:00 o'clock on these two days. However, it will be possible for members to attend the program of Dry Clinics from 9:00 a.m. to 10:00 a.m. and attend the Round Tables from 10:00 a.m. to 12:00 m.; or it will be possible for members to attend the full program of Dry Clinics and elect Round Tables from 11:00 a.m. to 12:00 m. on these days.

The outline of Round Table Conferences and the leaders follows. The hours and room designations at the Municipal Auditorium will appear in the formal program:

CARDIOLOGY	Fred M. Smith, Iowa City, Iowa.
NUTRITION	James S. McLester, Birmingham, Ala.
NEPHRITIS	Wm. S. McCann, Rochester, N. Y.
BLOOD	R. R. Kracke, Emory University, Ga.
X-RAY	B. L. Kirklin, Rochester, Minn.
SULPHANILAMIDE, BACTERIAL CHEMOTHERAPY	P. H. Long, Baltimore, Md.
GASTRO-ENTEROLOGY	Lay Martin, Baltimore, Md.
PNEUMONIA	H. A. Reimann, Philadelphia, Pa.
SURGERY	Irvin Abell, Louisville, Ky.
DIABETES (Metabolic Diseases)	Elliott P. Joslin, Boston, Mass.
PEDIATRICS	A. F. Hartman, St. Louis, Mo.
ENDOCRINOLOGY	Elmer L. Sevringhaus, Madison, Wis.
PHYSIOLOGY	Carl A. Dragstedt, Chicago, Ill.
PSYCHO-SOMATIC MEDICINE	W. R. Houston, Austin, Tex.
PARASITOLOGY	E. C. Faust, New Orleans, La.

PROGRAM OF SPECIAL CLINICS AND DEMONSTRATIONS

Practical Hospital Clinics and Demonstrations will be held from 9:00 a.m. to 12:00 m., Tuesday and Thursday mornings (March 28 and 30), instead of each of four mornings as the custom has been heretofore at the Annual Sessions of the College. However, programs of Dry Clinics will be conducted in the main meeting hall of the Municipal Auditorium from 9:00 a.m. to 11:00 a.m. on Wednesday and Friday mornings, thus supplementing the program of Hospital Clinics and Demonstrations.

Most of the Clinics and Special Demonstrations ("A," "B," "C") will be given at the Charity Hospital by the Tulane and Louisiana State University Medical School faculties. There will be three clinics and demonstrations carried on at this place. In addition to local men, a few out-of-town visitors will participate, such as Dr. Hugh Morgan, Nashville, Tenn.; Dr. Charles H. Cocke, Asheville, N. C.; Dr. James S.

McLester, Birmingham, Ala.; Dr. Samuel F. Haines, Rochester, Minn.; Dr. James E. Paullin, Atlanta, Ga. One of the features at the Charity Hospital clinics will be a daily clinico-pathologic conference which Dr. Joseph R. D'Aunoy, the Pathologist and Professor of Pathology, will conduct with some visiting clinician.

The Tulane University Clinic "D" will include not only the exhibition of patients, but also the demonstration of research work that is being conducted by the School. Clinic "E" will be held at Touro Infirmary, and will include demonstrations and clinics by members of the staff of this notable institution, together with a certain number of invited guests, including Dr. A. A. Herold, of Shreveport; Dr. Seale Harris, of Birmingham; Dr. Reginald Fitz, of Boston; Dr. R. H. Kampmeier, of Nashville; and Dr. Irving Gray, of Brooklyn. Clinic "F" will be held at the Baptist Hospital, where Dr. L. F. Bishop, Jr., of New York, will be one of the guest speakers. Clinic "G" will be held at Hotel Dieu, where Dr. F. W. Willius, of the Mayo Clinic, will be the out-of-town visitor. Clinic "H" will take place at the U. S. Marine Hospital, where, in addition to distinguished members of the U. S. Public Health Service, there will be invited to participate Dr. N. W. Barker, of the Mayo Clinic, and Dr. Walter M. Simpson, of Dayton, Ohio.

Demonstrations will be held in the Hutchinson Clinic for a small group of men on Tuesday and Thursday mornings. These will include research work and demonstration of special methods applicable to clinical medicine.

Admission will be by ticket only, otherwise crowding of the clinics and wards will interfere with effective demonstration of cases. To all members of the College registration blanks for the clinics and demonstrations will be distributed with the formal program. These registration blanks should be filled out and returned to the Executive Secretary of the College, who will select the proper tickets and hold them for members at the Registration Bureau at New Orleans. Reservations by mail cannot be made after March 20, but they may be made in person at the Registration Bureau on the evening preceding any clinic day. Guests will kindly register for clinics at the Registration Bureau upon arrival at New Orleans.

NEW ORLEANS—WHERE WE MEET

THE history of New Orleans is not only a chronicle of material advancement, it is also a record of the progress of medical and surgical heroes. It is a saga of a titanic warfare fought by feeling individuals interested in human welfare and of employment of the implements of science for expediency's sake.

New Orleans is famed for the beauty of its women, for its chefs, its foibles and failures, and most of all, for the unbounded hospitality of its Mediterranean civilization. There are few, however, who are familiar with the gigantic combat waged by its medical men through the centuries which has lifted a struggling community out of a miasmic swamp and made it one of the great ports of the world.

One must be reminded that the city has been visited by thirty-nine yellow fever epidemics. One of these claimed two-thirds of the city's residents. For generations its cobble stone streets rumbled with the clatter of dead wagons. Without the aid of telegraphic communication the world was never acquainted with the fact that it suffered two fires both equalling in magnitude the Chicago conflagration. The raging Mississippi has swept away its homes on countless occasions. Its people have been visited by the bubonic plague and a hundred other kindred diseases of a semi-tropic land. It has suffered famine and the ravages of war and has been occupied by invaders from its own and foreign shores. Ten flags have been raised over its surrounding dank marshes and broad fields of sugar cane.

The city's giant skyscrapers of today, its pumps which keep a community located 13 feet below sea level a healthy place in which to live, its tremendous levees holding back the mighty Mississippi are not only measures of the engineering skill or foresight of pioneers but are also monuments to its intrepid men of medicine, unheralded and unsung, who have aided in making it the metropolis of the Southern Empire.

New Orleans was founded in 1718 by Jean Baptiste Le Moyne, Sieur de Bienville, one of the greatest French colonizers. He chose the site of the town, which he hoped would eventually become capitol of the vast colony of Louisiana, on a slightly higher level of ground nestling in a great sweeping curve of the Mississippi river a little more than a hundred miles from its mouth.

Because French ministers were unable to visualize the possibilities of the site, and refused to coöperate with Bienville in developing it, the first few years of the city were not very promising. Father Charlevoix, one of the first visitors to the struggling settlement, wrote in 1722 that it consisted of a hundred barracks, a large wooden storehouse, a few tents and two or three houses, which, he observed, " would be no ornament to a village of France."

In that same year, however, Bienville, backed by Adrian de Pauger, finally succeeded in obtaining funds. From this date the city's rise began.

De Pauger, who was assistant to Le Blond de la Tour, Royal Engineer, drew up the plans for the city according to the French style. It was built within a wall, protected on three sides by a moat and on the fourth by the Mississippi river.

De Pauger marked out a square around which important public buildings of the new community were to be located and from which the city was to build out. The square was called the Place D'Armes. In 1849 its name was changed to Jackson Square in honor of the hero of the Battle of New Orleans.

The beginnings of New Orleans are still to be found in an area which the city has long since outgrown and which is known as the French Quarter, Old Quarter or Vieux Carré.

This French Quarter, the most famous single thing about New Orleans from the visitor's point of view, is very much the same now in appearance as it was towards the end of the French and Spanish dominations in the late seventeen hundreds. It is in fact a veritable treasury of historic lore—romantic and picturesque. Its exquisite wrought-iron railings, straight narrow streets, quaint architecture, fan windows and charming patios or courtyards are a never-ending source of fascination.

Recorded medical history in New Orleans begins as romantically as its first material advancement. More than 200 years ago it began with the death of a sailor, Jean Louis, a native of the city, who left the following document to the people of Louisiana.

"Nothing being more certain than death, and nothing more uncertain than its hour, being stricken with a dangerous bodily malady, but of sane mind, I desire to settle my affairs, explaining how my last will shall be carried out by my testimentary executor.

"I give to the poor of New Orleans, who are ashamed to beg, two hundred livres and also one hundred livres to procure clothes for the most needy orphans at my executor's pleasure.

"My debts having been paid and the above provisions having been executed, a sale shall be held of all that I own, the proceeds of which, together with the other monies I own, I bequeath to serve in perpetuity to the founding of a hospital for the sick of the city of New Orleans and to secure the things necessary for the sick."

Jean Louis' legacy totalled 10,000 livres. With this fund Bienville erected and equipped a hospital called the St. John's hospital or L'hospital de Pauvres de Charité or Charity Hospital.

This institution flourished for 40 years although there is no written record of the work of those brave doctors who administered to the victimized settlers roaming Louisiana's endless fever-infested swamps in search of John Law's Utopia, which had ended in the Mississippi Bubble debacle.

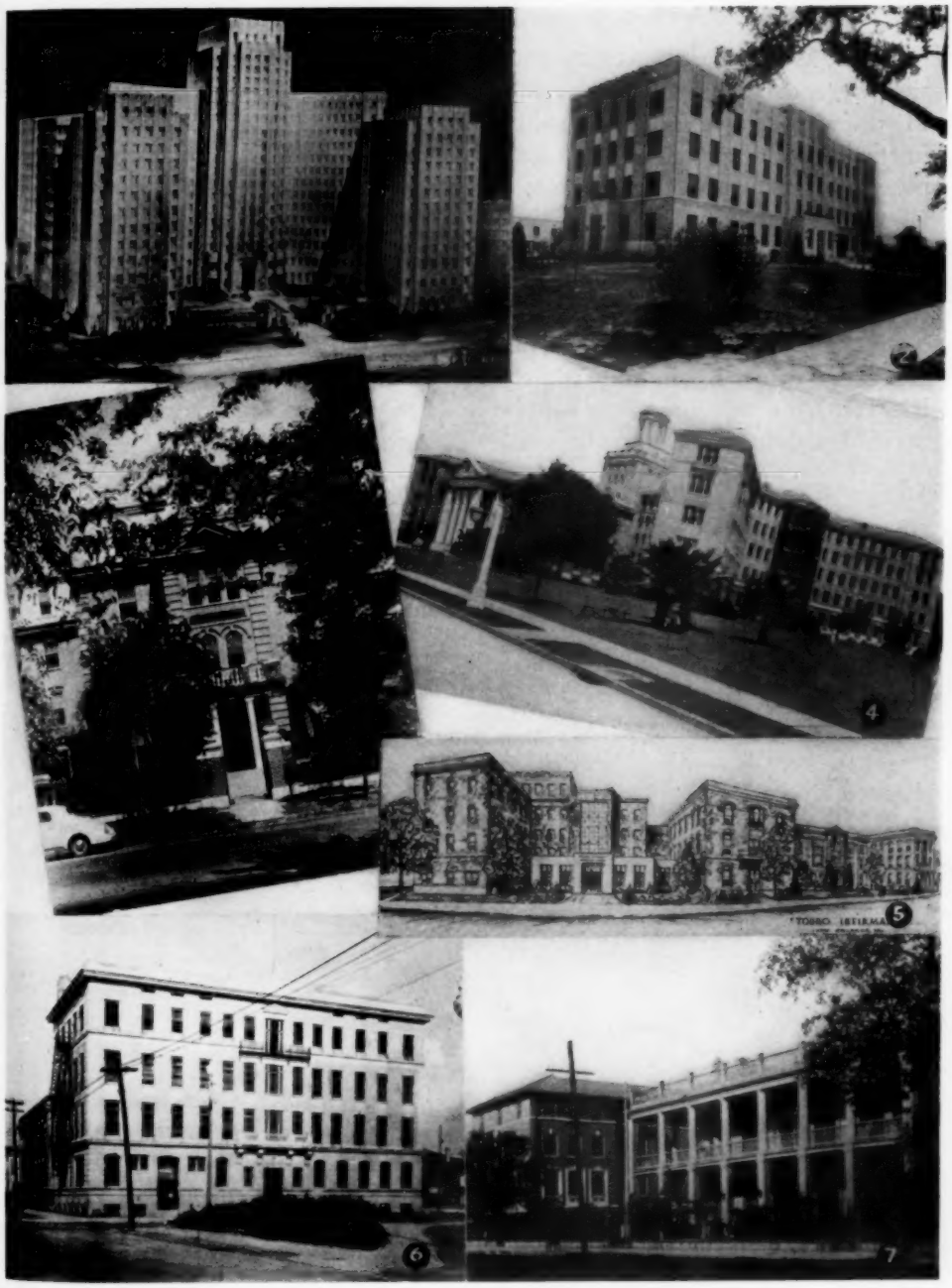


FIG. 1.

No. 1. New Charity Hospital.
No. 2. Flint-Goodridge Negro Hospital.
No. 3. De Paul Sanitarium.
No. 4. U. S. Marine Hospital.
No. 5. Touro Infirmary.
No. 6. Eye, Ear, Nose and Throat Hospital.
No. 7. Mercy Hospital. Columned building in foreground is administration formerly old plantation mansion of the Soniat du Fossat plantation.

In 1779 a hurricane carried away the hospital of Jean Louis and the sick were driven into the streets. At that time Governor Don Estevan Miro wrote King Charles of Spain: "Many sick paupers are now wandering in the streets of your city in quest of shelter and aid. They are hourly exposed to perish in the very streets or die in some obscure corner."

One can imagine that at the time doctors' fees were none too high, if any at all were charged. We are told that at the time each physician carried all of his own instruments and medicines. There were but four apothecaries in the city.

Touched by the widespread misery, Don Andres Almonaster y Roxas, a grandee of old Spain and former high ranking royal army officer, donated $140,000 for rebuilding the hospital. It took King Charles until 1782 to accept the donation and the hospital was finally built.

FIG. 2. Louisiana State University Medical Center. Ground in the foreground had been cleared to make room for the new $12,000,000 Charity Hospital. The Medical center is on the grounds of Charity hospital.

On September 23, 1809, a fire leveled half of the city which had escaped a fire in 1788 and the city's only refuge for the sick was again wiped away.

Writers of the day draw a pitiful picture of the sufferings of the poor during the severe winter which followed the fire. The following year, a yellow fever epidemic swept the city. For five years the community, swarming with hordes of adventurers and mariners from all over the world, remained without a hospital. Physicians were obliged to treat the sick at hotels, in public buildings and often take them into their own residences.

In the meanwhile, Don Almonaster had died. Richest man in the colony, lawyer, statesman, contractor, architect and soldier, he was laid beneath a slab in the St. Louis Cathedral. On June 9, 1811, Micaela Almonaster, his only daughter, became the Marquese de Pontalba and, as a parting gift to

Louisiana as she left for France, gave to the state her rights as patroness of the corporation of New Orleans and the Charity Hospital.

As the eighteenth century came to a close Spain began to decay. Louisiana was again in the possession of France, and Napoleon, knowing he could not protect it from the British, sold the territory to the United States. Foreign aggression which had been holding the city down as a port of debarkation was removed and New Orleans skyrocketed to prosperity.

Craft of every description poured down the river. The population doubled, then trebled. Public buildings were erected, and the cornerstone for a greater Charity hospital was laid.

FIG. 3. The Hutchinson Memorial Building, headquarters of the School of Medicine of Tulane University. It is across the street from the new $12,000,000 Charity Hospital.

Space does not permit the outlining of a history of those institutions which have followed Charity Hospital. Their work is evidenced by the general good health of the residents of the city. By the fact that although the city draws its water supply from the muddy Mississippi, it has the purest drinking water in the world and its death rate is low in comparison with other cities of its size.

In citing work of New Orleans physicians in the field of science, we can quote from no better source than the New Orleans City Guide, a Federal Workers Project, summarizing information on the city, which has been edited by Lyle Saxon, Louisiana's historian and writer. With permission, we quote from the guide:

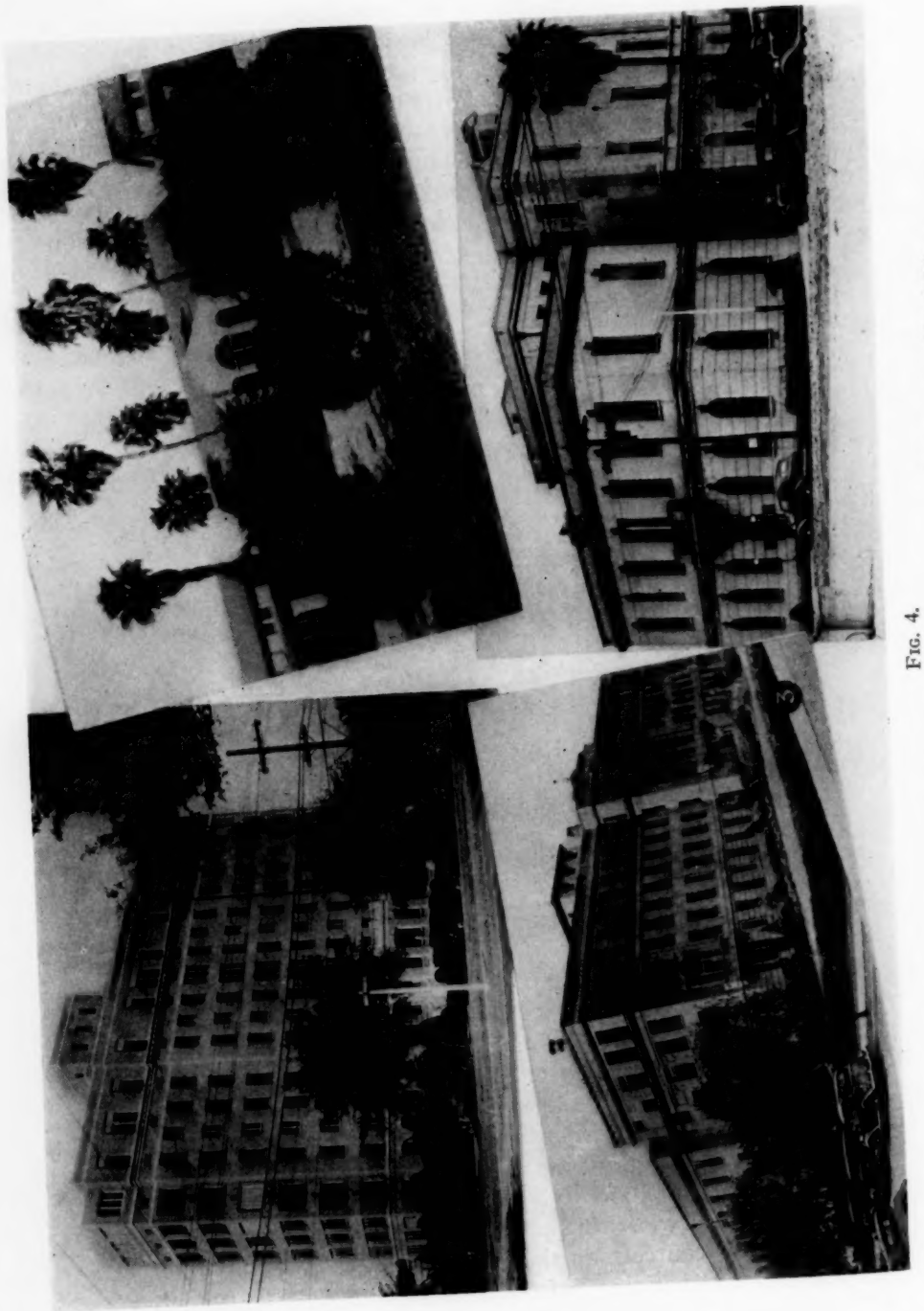


FIG. 4.

Upper Right—Orleans Tuberculosis Hospital.
Upper Left—Baptist Hospital.
Lower Left—Hotel Dieu.
Lower Right—French Hospital.

" New Orleans has long served as a proving ground for applied science. In overcoming problems arising from the soggy nature of the subsoil, the low elevation of the city, climatic conditions favorable to malignant diseases, and the danger of Mississippi flood waters, New Orleans has made many contributions to scientific advancement.

" Noteworthy work has been done in medicine, especially in the control of yellow fever, malaria, cholera, smallpox, hookworm, and dysentery—diseases which once, because of climatic conditions, lack of adequate sewage disposal, and poor drainage, proved a scourge to the city. They are now under control and the danger of epidemics is minimized.

" Although the discovery of the causative agent of yellow fever was made elsewhere, many of the problems of practical control in large cities were solved in New Orleans by local physicians. Samuel Chopin, C. B. White, A. W. Perry, and others introduced quarantine and disinfecting methods which, though the carrier of the disease was unknown at the time, were instrumental in checking the fearful toll of yellow fever epidemics. Dr. Charles Faget contributed an indispensable diagnostic sign of yellow-fever—a fall in pulse rate during the first days of the disease."

In other fields of medicine New Orleans physicians and surgeons have done much pioneer work and have made many important contributions: C. C. Bass and F. M. Johns, cultivation of the plasmodium of malarial fever; A. W. De Roaldes, establishment of the first eye, ear, nose, and throat hospital in the South; Ernest S. Lewis, pioneer work in gynecology; C. A. Luzenburg, removal of a gangrenous bowel in hernia: J. L. Riddell, invention of the binocular microscope; H. D. Schmidt, demonstration of the origin of bile ducts in intercellular spaces; A. W. Smyth, ligation of the innominate artery; Warren Stone, work on aneurysm, and resection of a rib to secure permanent drainage in empyema. Dr. Edmond Souchon developed two methods of retaining the color of muscles and organs in the preservation of anatomic dissections; the curing method using arsenic, calcium chloride, and formol; and the physical or paint method by which colorless muscles in a dissection are given permanent color. In addition to founding the Souchon Museum of Anatomy at Tulane University, he did much original work on aneurysm of the sub-clavian artery and aorta. Dr. Rudolph Matas, world-famous surgeon, has made many contributions to surgery, especially to vascular surgery, as well as a method of reducing and securing fixation of zygomatic fractures, an original method of blocking nerves in regional anesthesia, and the application of spinal subarachnoid anesthesia for surgical purposes. Valuable contributions to medical knowledge have also been made by Caine, Bruno, Jamison, Couret, Parham, Martin, and Lynch.

In dentistry, Dr. Edmund C. Kells, about thirty-five years ago, was the first to employ the roentgen-ray in his profession. A recent noteworthy accomplishment in dentistry was the method devised by Dr. S. C. Fournet and his assistant, C. S. Tuller, for stabilizing and retaining lower dentures.

Upper Right—Orleans Tuberculosis Hospital.
Upper Left—Baptist Hospital.
Lower Right—French Hospital.

The Loyola Dental School, established in 1914, is rated as a class A dental school, and is one of the best equipped institutions of its kind in the South.

In Charity Hospital New Orleans has one of the finest medical institutions in the country. Almost every physician in the city and a number practising in the neighboring parishes do part-time work at the hospital. The Medical Schools of Tulane and Louisiana State Universities train their students at the hospital and carry on much valuable research. Both medical schools rank with the best in America. The Tulane Medical School began in 1834 as the Medical College of Louisiana and merged in 1845 with the University of Louisiana, forerunner of Tulane University. In the Department of Tropical Medicine much important research is carried on in tropical diseases. The Medical Center of Louisiana State University, established in 1932, is domiciled on Charity Hospital grounds and has all the facilities of the hospital at its command. It is one of the few medical schools in the country requiring a fifth year of internship. The Flint-Goodridge Hospital is one of the South's leading hospitals for Negroes.

Principal centers of medical interest in New Orleans are:

Hotel Dieu, 2004 Tulane Avenue, conducted by the Catholic Order of Daughters of Charity of St. Vincent de Paul, better known as the "Sisters of Charity." It is one of the oldest private institutions in Louisiana. It was founded in 1852 in a residence owned by Dr. Warren Stone and acquired its present name and site in 1858. The hospital has 175 beds, 110 nurses in training, and six resident interns in attendance.

Charity Hospital, maintained by the state for the benefit of indigent citizens. It is at present being rebuilt and at its completion it will be one of the best equipped institutions of its kind in the United States. The buildings cover an area of three blocks fronting on Tulane Avenue. In addition to the main group of buildings, there are a number of other buildings in use, which include two structures used for repair shops, ambulance garage, and a dormitory for interns and residents.

The new main building will house 2,200 patients. To man it there will be required over 500 nurses, 190 interns and approximately 100 residents, as well as a large staff of physicians and surgeons. The building program also includes a new Nurses' Home and a number of service buildings.

Free clinics for both white and negroes are maintained as well as an accident ward open at all hours for emergency cases. Outpatients receive dental as well as medical treatment of every sort through clinics staffed by volunteer doctors. Senior students of Tulane and Louisiana State Universities are taught in these clinics.

Approximately $1,500,000 is spent annually in the operation of the hospital. This sum is gathered largely from state appropriations, and is supplemented by numerous large gifts and the increment from trust funds left to the institution during the past 200 years.

The City Hospital for Mental Diseases is housed in a three story brick building at South Broad and Perdido Streets. It was erected in 1911

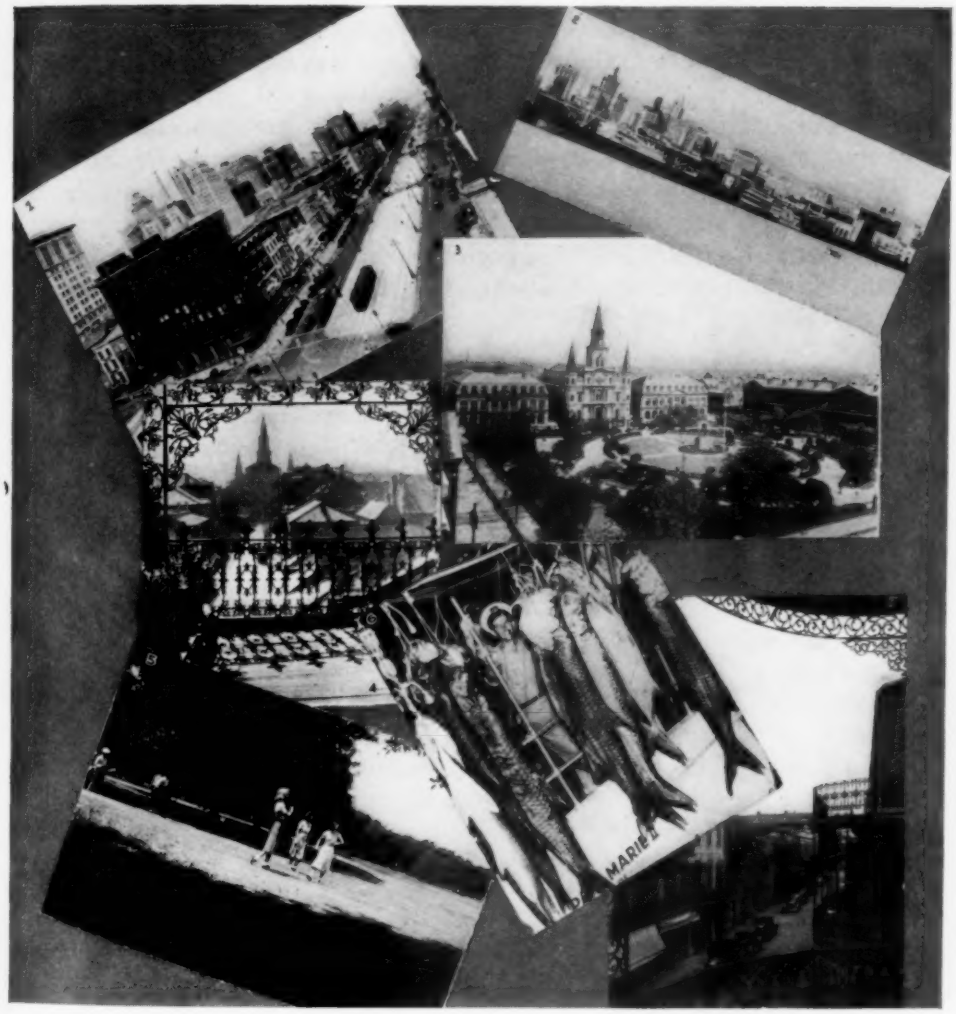


FIG. 5.

1. Historic Canal Street in New Orleans. Said to be the widest business thoroughfare in the world. The sidewalks are of pink and white terazza trimmed with brass.
2. New Orleans business district from the Mississippi.
3. The Place D'Armes or Jackson Square. Formerly the heart of New Orleans and spot where the transfer of Louisiana from France to the United States took place. On the right of the Cathedral of St. Louis, center, is the Archbishop's Palace and on the left is the Cabildo or seat of the colonial government of the territory. The long building on the right is the Pontalba Apartments, first apartment house in America.
4. Roofs of the historic Vieux Carre.
5. Audubon Park golf course, one of the city's many.
6. Fish abound all around New Orleans, in Lake Pontchartrain and in the bayous and canals.
7. The Vieux Carré is famed for its beautiful architecture and wrought iron balconies.

and has accommodations for 100 patients. Barred from hospitals, the mentally diseased were inadequately cared for. They were frequently confined to the city jails until the year 1880 when this hospital was established to house them.

LOUISIANA STATE UNIVERSITY PATHOLOGICAL MUSEUM, 1556 Tulane Avenue. Part of the LSU Medical Center contains about 1,000 mounted specimens of the most common lesions of all the anatomical systems of the body. Each specimen is accompanied by a mounted photomicrograph showing characteristic changes. A complete abstract of the clinical history, physical examination and postmortem findings in other organs in the disease process is cataloged for reference.

MUSEUM OF THE DEPARTMENT OF TROPICAL MEDICINE, at Tulane University, is located on the fifth floor of the Hutchinson Memorial Building, 1430 Tulane Avenue, regarded as one of the best in America.

Among important exhibits to be seen are those of malaria, leprosy, intestinal protozoa, plague, yellow fever, tropical diseases of the skin, venemous snakes and disease-transmitting insects and worms.

THE CHARLES EDMUND KELLS DENTAL MUSEUM AND LIBRARY, Hutchinson Memorial, Tulane University, Library second floor, Museum sixth floor. The library has 1,000 volumes dealing with dentistry. The museum contains 15 cases displaying instruments, teeth, plaster models and skulls complete.

EYE, EAR, NOSE AND THROAT HOSPITAL, 116 Elk Place, occupies two buildings. Established in 1889 by Dr. A. W. DeRoaldes, for "those too poor to pay." There are 70 beds, some are used for pay patients. Funds for operation are derived from small allottments from the State and city and from donations from citizens and payment by private patients. The staff of the hospital is composed of doctors of the city who donate their services.

TOURO INFIRMARY is a private institution under Jewish management. It is non-sectarian in its work. It operates a general clinic for both white and negroes. There are 350 beds. It was founded in the 1840's by a Jewish philanthropist Judah Touro.

MERCY HOSPITAL-SONIAT MEMORIAL HOSPITAL, 1312 Annunciation St. Founded in 1924 and operated by the Sisters of Mercy (Catholic Order). The main building is the old Soniat Plantation home, erected about 1816 on ground that was once the great Jesuit plantation where sugar cane was first introduced into America. It houses 115 beds, averages 51 nurses in training, 4 resident interns and 125 city doctors. A free clinic for white persons only is operated under auspices of the Community Chest. An average of 17,000 patients are treated free.

BAPTIST HOSPITAL, 2700 Napoleon Avenue, a nine-story brick building housing 198 beds. Constructed in 1926. There is a two-story brick building directly behind the main hospital, which is used as a nurses' home. The hospital is operated under the supervision of the Baptist Convention.

ORLEANS TUBERCULOSIS HOSPITAL, 1931 Gentilly Road, cares for indigent persons with funds provided by the Community Chest. Capacity 100 beds; admittance to the hospital must come through the Orleans Anti-Tuberculosis League located at same address.

FLINT-GOODRIDGE HOSPITAL, 2425 Louisiana Avenue. A private hospital of 100 beds operated exclusively for Negroes. It has a four-story main building facing Louisiana Avenue and behind are two one-story structures used as a nurses' home and power plant.

DE PAUL SANITARIUM, Henry Clay Avenue and Magazine Street, is a private sanitarium for mental defectives. It adjoins historic Audubon Park.

U. S. MARINE HOSPITAL, established 1830 on site of plantation of pirate Jean Lafitte at Henry Clay Avenue and State St. Operated by the U. S. Public Health Service. It averages 430 patients tended by 11 medical and dental officers, 17 medical and dental interns, 55 nurses and 7 laboratory technicians. Thirteen outside specialists in various fields of medicine and surgery are available for consultation.

POST-CONVENTION CRUISE TO MEXICO CITY

(For itinerary, consult page 24, Advertising Section, of this Issue)

THE major Post-Convention Tour, following the New Orleans Session, will be to Mexico City. This descriptive matter supplements that appearing in the College News Notes Section, pages 900–902, of the December, 1938, issue of this Journal.

Lounge Car, Missouri Pacific.

Mexico is a decidedly foreign country and near home, yet fewer Americans have visited it than have seen Europe. Her ruins puzzle the archaeologists, there are more than hints of a one-time connection with Egypt, her scenery is lovely, her customs, language and architecture as different as you would expect in countries a thousand miles apart, her climate delightful.

The market places are always interesting whether you look or buy. Each is a riot of color and each a hubbub of commotion. On a main market day many a sleepy plaza is turned into a scene of animation, friendly and good-natured. Indians spread their wares along the ground. Oranges, tomatoes, pottery, corn and peppers mingle with gourds, with sturdy baskets, gay sarapes, toys that intrigue the adult as well as the child, puppets a few inches high, wistful, purple cows fashioned from clay and a thousand other familiar and unfamiliar articles.

Nearby is the old glass factory that has been in the same family for four generations. Here you can buy exquisite miniatures and see the famous Mexican bubble glass handblown and whirled from molten glass into finished pieces, not by artisans, but by artists.

Crafts from all parts of Mexico appear in the shops and markets of the capital. More glass from Guadalajara; lacquered boxes of olinala and

lacquered gourds; hand-tooled leather; fiber baskets with bands of black; pottery jugs and bowls with flowered decoration and many by Indians who spurn a potter's wheel.

Gold filigree jewelry, comparable to the best of the Florentine; jewelry of silver and old jade from the back streets of the capital; candlesticks, lamps and trays of hammered tin that needs no polishing; deep cream-colored pottery with strong designs in reddish brown from the mountain fastness; silver bracelets, plates and goblets, hand-hammered and etched in the tradition of ancient Toltec forebears.

Sarapes, heavy and rug-like or two-tone and light in weight; rebozos or shawls of cotton or of silk with a weave so fine they can be passed through a ring; sombreros of palmleaf fiber or with gold brocade; sashes in brilliant reds and blues; embroidery unequalled in workmanship and—oh—where shall we stop?

Market Scene.

From the steps of a modern office building one sees a sarape shrouded, sombrero-covered peon, rubbing elbows with men whose clothes bear the stamp of Broadway. Down the avenue swaggers a grandee from a distant ranch, clad in a romantic-looking charro suit of leather. Rebozo-covered Indian women sell exquisite drawn work to senoritas dressed in the height of Parisian fashions. A liveried chauffeur pilots an imported car to one side to make room for an ox-drawn cart that creaks of a century of use. On every hand are quaint pictures of native life, of whimsical activities and customs. Mexico City is rich with its own individual and characteristic brand of "local color"—an intriguing mixture of the old and the new, of the glories of Old Spain and of the new world progress.

Cuernavaca is a picturesque and delightful city with a mingling of the old and the new. Its streets are narrow, cobblestoned, and clean; some of them are flanked by fruitladen mango trees or flowering Bougainvillea. It

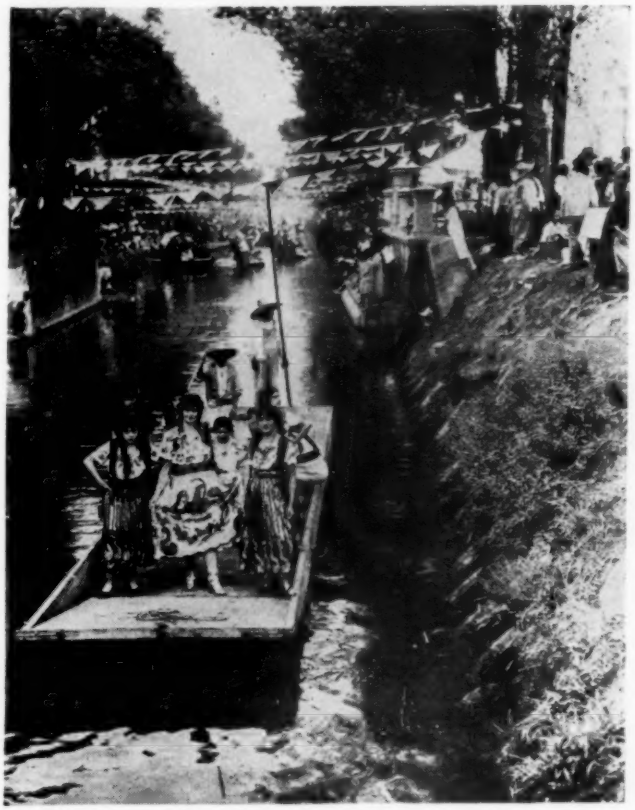
abounds in beautiful modern homes and is a favorite retreat of residents of Mexico City. Here was the home of the late Dwight W. Morrow. It commands a lovely view of the valley. The semi-tropical climate, cool breezes, and perpetual sunshine, even before the Spaniards conquered Mexico in the 16th century, lured nobles to Cuernavaca. Montezuma was often a visitor, Cortez built a palace there; Emperor Maximilian and Carlotta chose the Borda Gardens for their summer home; Presidents and Ambassadors have built their country mansions there.

Mexican Street Scene.

Cholula, known as " The Holy City of Anahuac " is of unfailing interest because of its large number of picturesque and quaint churches. Here is the famous convent of San Francisco where history says was celebrated the first mass in Mexico. The crowning feature of Cholula is the church on the pyramid built in the 16th century. From the stone-covered church yards if the day is clear we can see the twin peaks of Popocatepetl and Ixtaccihualt and the peak of Orizaba.

Guadalupe is the site of the most sacred shrine in Mexico, erected to Our Lady of Guadalupe on the spot where she appeared before the Indian, Juan

Diego, in 1531 and converted his sarape into a beautiful cloth bearing her image. This cloth is still preserved in a frame of pure gold and enclosed by a solid silver rail. The present Basilica, at the foot of Tepeyac Hill, has a beautiful interior and is the Mecca of Mexicans, visited annually by thousands of pilgrims.



Floating Gardens.

Xochimilco is a mecca because of the mystic beauty, the charm and uniqueness of the so-called "Floating Gardens." Once an Indian stronghold, it is now a new world Venice and Bangkok combined. We shall have a voyage between tiny flowered islands in a flat-bottom boat, punted by long poles in the hands of native Indians. In no place on the earth can such an experience be duplicated.

Puebla has been called "The Rome of Mexico." More than fifty interesting churches include a magnificent Cathedral unrivalled in its decorations; onyx pillars, wood-carvings, mosaics, paintings, etc., and the church of Santo Domingo which has untold riches in Churrigueresco decoration. Puebla is one of the oldest cities in Mexico and has preserved many of the architectural gems of its colonial epoch.

Pyramid of the Sun.

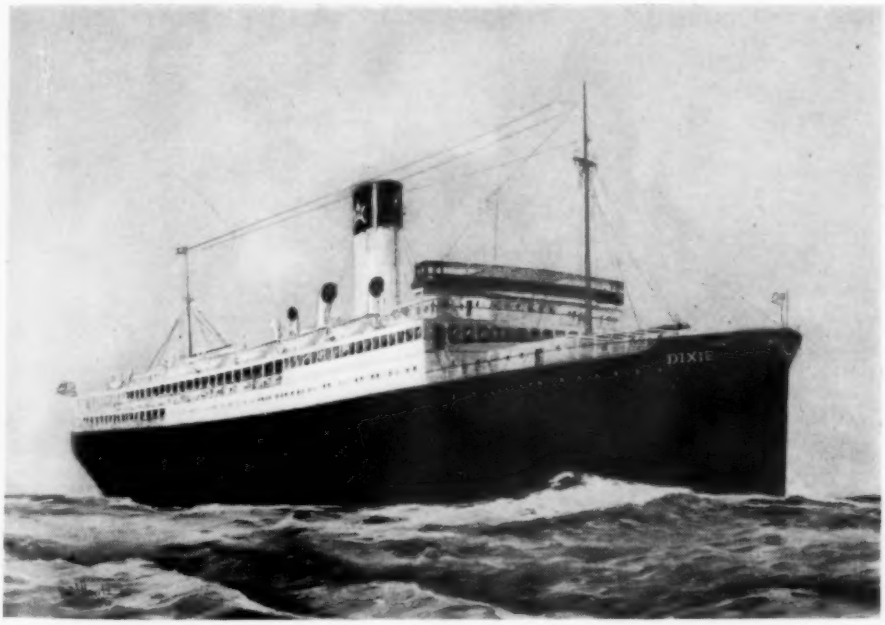
San Juan Teotihuacan and the Pyramids

The ancient Pyramids of the Sun and the Moon at San Juan Teotihuacan are the largest artificial mounds on the continent, and the one of the Sun closely rivals the pyramids of Egypt in area and height. They mark the site of a city so ancient that there is no authentic record of when or by whom it was built. The Buried City, revealed by modern excavations, was probably built some 3000 years ago; the walls and stairways of the large rooms have polychrome decorations and are presumed to have been the palace of the ruler of the ancient inhabitants. You will be entranced with these evidences of an unknown civilization here on our own continent. You may climb the steps of the pyramid and feel like an Aztec Emperor dominating the valley at your feet. See the colored frescos on the walls of the tunnels, climb over the mounds. Who were these people, the builders? The answer is still "Who?" for though much has been written, mystery for the most part enshrouds their origin and life.

These are only a few of the interesting sights that we shall see on our motor excursion in and around the city. We have neglected Mexico from a travel angle. We, the people of the United States, have just discovered our neighbor.

AFTER NEW ORLEANS—BACK TO NEW YORK BY WATER

When the Twenty-Third Annual Session of the College at New Orleans is over, those from the East and the Northeast, or even from the Middlewest, who may not choose to accompany the special party on the Mexico City post-convention tour, but who still may desire some post-convention diversion, should consider returning from New Orleans to New York City via the *S.S. Dixie,* leaving New Orleans at 11:00 a.m., April 1, and arriving in New York City at 8:00 a.m., April 6. The cruise conductor for the College, Mr. Leon V. Arnold, 36 Washington Square West, New York City, has reserved a number of accommodations to take care of members of the College. In fact, some may wish to use the *S.S. Dixie* in both directions, and Mr. Arnold will see that proper accommodations will be provided promptly upon application to him.



The S.S. Dixie

On the *Dixie* many of the staterooms and suites are provided with private tub and shower baths and toilets, and all the suites and staterooms are outside, facing the sea. The passenger quarters are of American Colonial design, and public rooms include a dining salon, handsome lounge, library and music room; observation sun parlor and dance room; smoking room and modern bar; barber shop; and a commodious built-in outdoor swimming

pool. There is hot and cold running water in all the rooms, and hot and cold fresh and salt water is supplied to all baths. All the rooms have electric fans, thermos bottles for drinking water, wardrobes and full-length mirrors.

Some members will wish to extend the Convention period into a holiday period. The *Dixie* makes it possible to enjoy the good fellowship of old friends and new in either or both directions for " one hundred golden hours at sea."

On the southbound journey, after passing Sandy Hook on the *Dixie,* the attractive Jersey coast with its famous resorts is kept in view until Atlantic City is passed during the night of the first sailing day. At about six o'clock the next evening, when off Hatteras on the coast of North Carolina, the steamer's course is shaped across the Gulf Stream—that mysterious and vast ocean current that issues out of the Caribbean Sea and the Gulf of Mexico.

A change from the deep blue of the Gulf Stream to the emerald green of the open sea discloses to the voyager that only a few hours were consumed in crossing the Stream. It is entered again when the vessel is near Matanilla Reef and the Great Bahama Islands. Then, about 2:00 p.m., three days after leaving New York, Jupiter Light on the coast of Florida is sighted.

The ship's course is now lying only a few miles off shore and the Florida coast is kept in sight during the remainder of the day, affording a clear view of the Florida resorts, including Palm Beach and Miami. An interesting succession of beacon lights is strung along the coast, interspersed here and there with stretches of glittering highways, village and resort lights, that present a brilliant and fascinating spectacle as the steamer proceeds down the coast during the night.

Early the next morning Sand Key, the southernmost point in the United States and within 57 miles of the line of the Tropics, is passed. And now we see Key West in the distance. Then we pass Rebecca Shoals Light, Garden Key—on which Fort Jefferson is located—and Dry Tortugas, after which the course is shaped northwesterly across the Gulf of Mexico. The sunsets here are beautiful as vast white clouds pile up in fantastic shapes and the setting sun makes the water gleam like gold while the whole range of visibility is suffused with a purple glow. Twice is this view possible, for the transit of the Gulf includes the evening hours of two days.

South Pass, at the Delta of the Mississippi River and one of the strangest marine gateways in the world, is made at about nine o'clock on the last night. Here the river pilot is taken aboard to direct the ship up the 105 miles of the Mississippi River to the pier in New Orleans, which we reach at seven o'clock in the morning.

Northbound the route is in reverse and equally as alluring and delightful.

For all information, plan of the ship, reservations, etc., write to Mr. E. R. Loveland, Executive Secretary, the American College of Physicians, 4200 Pine St., Philadelphia, Pa., or Mr. Leon V. Arnold, 36 Washington Square West, New York City.